Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis (Review)

Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Maxwell LJ, Buchbinder R, Lopez-Olivo MA, Suarez-Almazor ME, Tugwell P, Wells GA

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[Overview of Reviews]

Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis

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A B S T R A C T

Background

Biologic disease-modifying anti-rheumatic drugs (DMARDs: referred to as biologics) are effective in treating rheumatoid arthritis (RA), however there are few head-to-head comparison studies. Our systematic review, standard meta-analysis and network meta-analysis (NMA) updates the 2009 Cochrane overview, 'Biologics for rheumatoid arthritis (RA)' and adds new data. This review is focused on biologic or tofacitinib therapy in people with RA who had previously been treated unsuccessfully with biologics.

Objectives

To compare the benefits and harms of biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) and small molecule tofacitinib versus comparator (placebo or methotrexate (MTX)/other DMARDs) in people with RA, previously unsuccessfully treated with biologics.

Methods

On 22 June 2015 we searched for randomized controlled trials (RCTs) in CENTRAL, MEDLINE, and Embase; and trials registries (WHO trials register, Clinicaltrials.gov). We carried out article selection, data extraction, and risk of bias and GRADE assessments in duplicate. We calculated direct estimates with 95% confidence intervals (CI) using standard meta-analysis. We used a Bayesian mixed treatment comparison (MTC) approach for NMA estimates with 95% credible intervals (CrI). We converted odds ratios (OR) to risk ratios (RR) for ease of understanding. We have also presented results in absolute measures as risk difference (RD) and number needed to treat for an additional beneficial outcome (NNTB). Outcomes measured included four benefits (ACR50, function measured by Health Assessment Questionnaire

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(HAQ) score, remission defined as DAS < 1.6 or DAS28 < 2.6, slowing of radiographic progression) and three harms (withdrawals due to adverse events, serious adverse events, and cancer).

Main results

This update includes nine new RCTs for a total of 12 RCTs that included 3364 participants. The comparator was placebo only in three RCTs (548 participants), MTX or other traditional DMARD in six RCTs (2468 participants), and another biologic in three RCTs (348 participants). Data were available for four tumor necrosis factor (TNF)-biologics: (certolizumab pegol (1 study; 37 participants), etanercept (3 studies; 348 participants), golimumab (1 study; 461 participants), infliximab (1 study; 27 participants)), three non-TNF biologics (abatacept (3 studies; 632 participants), rituximab (2 studies; 1019 participants), and tocilizumab (2 studies; 589 participants)); there was only one study for tofacitinib (399 participants). The majority of the trials (10/12) lasted less than 12 months.

We judged 33% of the studies at low risk of bias for allocation sequence generation, allocation concealment and blinding, 25% had low risk of bias for attrition, 92% were at unclear risk for selective reporting; and 92% had low risk of bias for major baseline imbalance. We downgraded the quality of the evidence for most outcomes to moderate or low due to study limitations, heterogeneity, or rarity of direct comparator trials.

Biologic monotherapy versus placebo

Compared to placebo, biologics were associated with clinically meaningful and statistically significant improvement in RA as demonstrated by higher ACR50 and RA remission rates. RR was 4.10 for ACR50 (95% CI 1.97 to 8.55; moderate-quality evidence); absolute benefit RD 14% (95% CI 6% to 21%); and NNTB = 8 (95% CI 4 to 23). RR for RA remission was 13.51 (95% CI 1.85 to 98.45, one study available; moderate-quality evidence); absolute benefit RD 9% (95% CI 5% to 13%); and NNTB = 11 (95% CI 3 to 136). Results for withdrawals due to adverse events and serious adverse events did not show any statistically significant or clinically meaningful differences. There were no studies available for analysis for function measured by HAQ, radiographic progression, or cancer outcomes. There were not enough data for any of the outcomes to look at subgroups.

Biologic + MTX versus active comparator (MTX/other traditional DMARDs)

Compared to MTX/other traditional DMARDs, biologic + MTX was associated with a clinically meaningful and statistically significant improvement in ACR50, function measured by HAQ, and RA remission rates in direct comparisons. RR for ACR50 was 4.07 (95% CI 2.76 to 5.99; high-quality evidence); absolute benefit RD 16% (10% to 21%); NNTB = 7 (95% CI 5 to 11). HAQ scores showed an improvement with a mean difference (MD) of 0.29 (95% CI 0.21 to 0.36; high-quality evidence); absolute benefit RD 9.7% improvement (95% CI 7% to 12%); and NNTB = 5 (95% CI 4 to 7). Remission rates showed an improved RR of 20.73 (95% CI 4.13 to 104.16; moderate-quality evidence); absolute benefit RD 10% (95% CI 8% to 13%); and NNTB = 17 (95% CI 4 to 96), among the biologic + MTX group compared to MTX/other DMARDs. There were no studies for radiographic progression. Results were not clinically meaningful or statistically significantly different for withdrawals due to adverse events or serious adverse events, and were inconclusive for cancer.

Tofacitinib monotherapy versus placebo

There were no published data.

Tofacitinib + MTX versus active comparator (MTX)

In one study, compared to MTX, tofacitinib + MTX was associated with a clinically meaningful and statistically significant improvement in ACR50 (RR 3.24; 95% CI 1.78 to 5.89; absolute benefit RD 19% (95% CI 12% to 26%); NNTB = 6 (95% CI 3 to 14; moderate-quality evidence), and function measured by HAQ, MD 0.27 improvement (95% CI 0.14 to 0.39); absolute benefit RD 9% (95% CI 4.7% to 13%), NNTB = 5 (95% CI 4 to 10); high-quality evidence). RA remission rates were not statistically significantly different but the observed difference may be clinically meaningful (RR 15.44 (95% CI 0.93 to 256.1; high-quality evidence); absolute benefit RD 6% (95% CI 3% to 9%); NNTB could not be calculated. There were no studies for radiographic progression. There were no statistically significant or clinically meaningful differences for withdrawals due to adverse events and serious adverse events, and results were inconclusive for cancer.

Authors' conclusions

Biologic (with or without MTX) or tofacitinib (with MTX) use was associated with clinically meaningful and statistically significant benefits (ACR50, HAQ, remission) compared to placebo or an active comparator (MTX/other traditional DMARDs) among people with RA previously unsuccessfully treated with biologics.

No studies examined radiographic progression. Results were not clinically meaningful or statistically significant for withdrawals due to adverse events and serious adverse events, and were inconclusive for cancer.

P L A I N   L A N G U A G E   S U M M A R Y

Biologics or tofacitinib for rheumatoid arthritis

Review question

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We studied the effects of biologics on people with rheumtoid arthritis (RA), whose previous treatment with biologic therapy was unsuccessful, either due to lack of benefits or occurrence of side effects, or both. There were a total of 12 studies (up to June 2015) with data available for four of the tumor necrosis factor (TNF)-biologics (certolizumab pegol, etanercept, golimumab, infliximab) and three of the non-TNF biologics (abatacept, rituximab, and tocilizumab); only one study provided data for tofacitinib.

What is RA and what are biologics/tofacitinib?

In RA, your immune system, which normally fights infection, attacks the joint lining making it inflamed. If the inflammation is untreated, joint damage and disability may result. Biologics and tofacitinib are medications that can reduce joint inflammation, improve symptoms and prevent some of the joint damage.

The review shows that in people with RA:

- Biologics alone or in combination with methotrexate (MTX), a disease-modifying anti-rheumatic drug (DMARD), improve signs (tender or swollen joints) and symptoms of RA, function, and probably improve the chances of RA remission (disappearance of symptoms), based on high- and moderate-quality evidence (downgraded for imprecision).

- Tofacitinib in combination with MTX, probably improves signs and symptoms of RA (tender or swollen joints) and function, based on high- and moderate-quality evidence (downgraded for imprecision).

- We often do not have precise information about side-effects and complications. This is particularly true for rare but serious side-effects. Because of the lack of data and low-quality evidence, we are uncertain of the effect of biologics and tofacitinib on the risk of cancer, serious adverse events, and withdrawals due to adverse events.

Best estimate of what happens to people with RA when taking biologics or tofacitinib:

ACR50*(number of tender or swollen joints, pain, and disability)*

Biologic monotherapy versus placebo: 18 out of 100 people on a biologic monotherapy experienced improvement in their symptoms versus 4 out of 100 on placebo (14% absolute improvement).

Biologic + MTX versus MTX/other traditional DMARDs: 21 people out of 100 on biologic + MTX experienced improvement in RA symptoms compared to 5 people out of 100 who were on MTX/DMARD (16% absolute improvement).

Tofacitinib + MTX versus MTX: 28 people out of 100 on tofacitinib + MTX experienced improvement in RA symptoms compared to 9 people out of 100 who were on MTX/DMARD (19% absolute improvement), based on one study.

Remission (DAS < 1.6 or DAS28 < 2.6)

Biologic monotherapy versus placebo: 102 people out of 1000 who were on biologic had their RA symptoms disappear compared to 8 people out of 1000 on placebo (9% absolute improvement).

Biologic + MTX versus MTX/other traditional DMARDs: 104 people out of 1000 who were on biologic + MTX had their RA symptoms disappear compared to 3 people out of 1000 who were on MTX/DMARD (10% absolute improvement).

Tofacitinib + MTX versus MTX: 56 people out of 1000 who were on tofacitinib + MTX had their RA symptoms disappear compared to 0 people out of 1000 who were on MTX/DMARD (6% absolute improvement), based on one study.

Progression of radiographic destruction

No studies were available for analysis.

Drug withdrawal due to adverse events

Biologic monotherapy versus placebo: 32 people out of 1000 on biologic reported withdrawal due to adverse events versus 42 out of 1000 on placebo (1% fewer withdrawals).

Biologic + MTX versus MTX/other traditional DMARDs: 38 people out of 1000 on biologic + MTX reported withdrawal due to adverse events compared to 8 out of 1000 people on MTX/DMARD (5% more withdrawals).

Tofacitinib + MTX versus MTX: there was no difference in withdrawals due to adverse events between people on tofacitinib + MTX and people on MTX/DMARD, both with 5 participants out of 100, based on one study.

Serious a*dverse events*

There was a 1% to 3% difference for fewer serious adverse events in all comparisons compared with people on MTX/DMARD.

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Cancer

Biologic + MTX versus MTX/other traditional DMARDs: there was a less than 1% difference for the risk of cancer between biologic + MTX and MTX/DMARD; 5 out of 1000 of those on biologic + MTX and 0 on MTX/DMARD developed cancer, although there were very few studies available.

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BACKGROUND

Description of the condition

Rheumatoid arthritis (RA) affects 0.5% to 1.0% of the population (Kvien 2004). RA is a systemic, autoimmune inflammatory arthritis that is characterized by inflammation of the synovial structure, including the joints, tendons and periarticular structures (Lee 2001). RA has a significant impact on health-related quality of life (HRQoL), function and can lead to physical disability (Kvien 2005; Lubeck 2004; Odegard 2005; Yelin 2007).

Various pharmacological treatment options are available for RA including the non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, traditional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine etc. and targeted therapies such as tofacitinib and biologics. With the exception of NSAIDs, which are a symptomatic treatment, all others listed are considered disease-modifying, that is, are associated with an improvement in pain, function and quality of life, and reduction of radiographic progression and long-term disability (Cash 1994; Finckh 2006; Pincus 2002; Strand 2008). When traditional DMARDs fail to improve symptoms in people with RA, biologics are one of the treatment options (Smolen 2014a; Singh 2012). Treatments with one or more biologics can be unsuccessful in some people and they may continue to have active symptoms. The RA patient population that has been treated unsuccessfully with biologics is the focus of this review.

Description of the interventions

Biologics are a new group of medications available for the treatment of people with rheumatoid arthritis and other forms of inflammatory arthritis. These drugs are manufactured using live cell systems. Biologics appear to have greater success in slowing structural joint destruction than traditional DMARDs, such as MTX, but are much more costly than the traditional DMARDs. In people whose treatment with traditional DMARDs has failed (also called DMARD/MTX-inadequate responders (DMARD/MTX-IR), biologics can provide improvements in pain and function. The use of biologics with traditional DMARDs has revolutionized the management of RA. The current available and approved biologics include the following.

1. Tumor necrosis factor (TNF)-inhibitors (Scott 2006): infliximab (Remicade, approved 1998 in the USA) (FDA 1999), etanercept (Enbrel, approved 1998) (FDA 1998), adalimumab (Humira, approved 2002) (FDA 2002), certolizumab pegol (Cimzia, approved 2008) (FDA 2008a), and golimumab (Simponi, approved 2009) (FDA 2008b)
2. Anti-interleukin (IL)-1 therapy: anakinra (Kineret, approved 2001) (FDA 2001)
3. Anti-B-cell therapy: rituximab (Rituxan/MabThera, approved 1997 for lymphoma and 2006 for RA) (Drugs 2006)
4. Anti-CD28 therapy: abatacept (Orencia, approved 2005) (FDA 2005; FDA 2008c)
5. Anti-IL-6 therapy: tocilizumab (Actemra, approved 2010) (FDA 2010)

An oral small molecule synthetic drug, tofacitinib (Xeljanz) (FDA 2012), was also approved in 2012 for use in people with RA, which is considered a different class by some, and a traditional targeted DMARD by others. Most biologics and tofacitinib are approved for use in RA internationally, although there are some differences in the indications for use between countries.

How the intervention might work

Biologics or tofacitinib work by inhibiting cells or pathways that are key to the pathogenesis of RA. Their targeted mechanism of action makes them effective therapies for RA. Systemic and joint inflammation in RA is mediated by activation and interaction of a variety of cells including the T-cells, B-cells, macrophages and other immune cells (Cope 2008; Szekanecz 2007; Woolley 2003), which leads to over-expression of pro-inflammatory chemokines, metalloproteinases and cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and various interleukins (IL) (Brennan 2008; Choy 2001) as well as bone and cartilage destruction by the interaction of pro-inflammatory cytokines and inflammatory cells with fibroblasts, osteoclasts and chondrocytes (Brennan 2008; Connell 2006). Due to different targets for biologics and tofacitinib, their efficacy or safety, or both, can potentially differ (see above, Description of the interventions). The RA treatment guidelines provide guidance regarding the use of biologics or tofacitinib, especially in patients unsuccessfully treated with a biologic (Saag 2008; Singh 2012; Singh 2016a; Smolen 2014a).

Why it is important to do this overview

People with RA whose treatment with biologics have failed form an important subgroup of people with RA, for whom effective and safe therapies are needed. According to the 2015 American College of Rheumatology (ACR) treatment guidelines for RA, another biologic or tofacitinib constitute a treatment option for such people (Singh 2016a). To our knowledge, no systematic review is available that addresses the treatment options for this patient population. Most of the existing Cochrane systematic reviews, provide a detailed review of each treatment option (Blumenauer 2002; Lethaby 2013; Lopez-Olivo 2008; Maxwell 2008; Mertens 2008; Navarro-Sarabia 2005; Ruiz Garcia 2014; Singh 2010a; Singh 2010b), but not a comparison of treatments to each other. Therefore, we need a systematic review and network meta-analysis (NMA) that can provide a side-by-side comparison of all treatment options for this patient population.

To our knowledge, head-to-head studies of biologics in people with RA whose treatment with biologics has failed have not been performed. Most studies to date that compared two biologics head to head, included people with RA with DMARD/MTX-failure who were biologic-naive (Gabay 2013; Schiff 2014a). We think that indirect comparisons can provide the best evidence for demonstrating any differences between the available treatments for the biologic-failure population, including biologics or tofacitinib (Kristensen 2007; Kristensen 2011). A common comparator can be used to make an indirect comparison (Song 2003).

We aimed to perform a systematic review, meta-analysis and NMA of treatment options for people with RA whose treatment with a biologic has failed. The NMA incorporates both direct and indirect comparisons. Thus, the resulting review differs from the usual systematic review, such that it systematically reviewed and simultaneously compared biologics or small molecule, tofacitinib for RA using data from the existing randomized trials (Becker 2008; Puhan 2014).

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New data have emerged since 2009, when we published the original overview and NMA of biologics for RA. We made an a priori decision to examine the use of biologics or tofacitinib in four RA populations separately, due to feasibility issues:

1. MTX/other DMARD-naive (under review; not yet published);
2. MTX/other DMARD-experienced (biologics or tofacitinib used concomantly with MTX/other DMARD) (Singh 2016b);
3. MTX/other DMARD-experienced (biologics or tofacitinib used as monotherapy) (Singh 2016c); and
4. Biologic-experienced (this review).

The other RA populations will be reported in separate Cochrane Reviews. This systematic review, meta-analysis and NMA focuses on RA patient population, who had been treated unsuccessfully with biologics.

OBJECTIVES

To compare the benefits and harms of biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) and small molecule tofacitinib versus comparator (placebo or methotrexate (MTX)/other DMARDs) in people with RA, previously unsuccessfully treated with biologics.

METHODS

Criteria for considering reviews for inclusion

NOTE: this update uses individual studies, not reviews, for the basis of all analyses

Randomized controlled trials (RCTs) of biologics or tofacitinib for RA in people who have been treated unsuccessfully with at least one biologic due to either lack of efficacy and/or the occurrence of side effects.

Types of studies

We included RCTs for any of the nine approved biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) or tofacitinib in people with RA, in any dose, if they reported clinically relevant outcomes (listed in the section below).

Types of participants

Adults 18 years or older, with RA, meeting the 1987 American College of Rheumatology (ACR) Classification criteria for RA (Arnett 1988) or the 2010 ACR/European League Against Rheumatism (EULAR) Classification criteria for RA (Aletaha 2010), who were biologic-experienced, that is, had been treated unsuccessfully with at least one biologic therapy or tofacitinib.

Types of interventions

Biologics or tofacitinib used alone or in combination with traditional DMARDs/other biologic compared to placebo alone or to placebo plus traditional DMARDs or biologics or combinations of DMARDs.

Types of outcome measures

Primary/major outcomes

1. ACR50 defined as 50% improvement in both tender and swollen joint counts and 50% improvement in at least three of the following five variables: patient global assessment, physician global assessment, pain score, Health Assessment Questionnaire (HAQ) score, and acute phase reactant (Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP)) (Chung 2006; Felson 1995). ACR50 was chosen, as clinical and statistical evidence supports this as the preferred endpoint for contemporary RA clinical trials (Ghogomu 2014). We realize the importance of ACR20 as clinical trial endpoint due to sample size considerations.
2. RA disease remission defined as DAS < 1.6 or DAS28 < 2.6 (Fransen 2005; Prevoo 1996).
3. Function measured by Health Assessment Questionnaire (HAQ) score or modified HAQ calculated as score changes (Fries 1980; Pincus 1983) and the proportion achieving minimal clinically important difference on HAQ ≤ 0.22 (Wells 1993).
4. Radiographic progression, as measured by Larsen/Sharp/ modified Sharp scores (Larsen 1977; Sharp 1971; Van der Heijde 1989).
5. Withdrawals due to adverse events (Ioannidis 2004)
6. Serious adverse events (SAEs) (Ioannidis 2004)
7. Cancer

We searched the US Food and Drug Administration (FDA) website for labels and warnings, since RCTs are limited in their ability to assess long-term safety, and rare or delayed effects are usually not evident/detected in RCTs. We also searched other regulatory agencies' web sites from Canada (Health Canada) and Europe (European Medicines Agency, EMA) to summarize warnings related to each of the biologics.

Search methods for identification of reviews

A Cochrane Information Specialist (TR) conducted an updated search to identify the individual studies in multiple databases including the Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Library, Issue 6, June 2015), MEDLINE (via OVID 1946 to June 2015), and Embase (via OVID 1947 to June 2015). We considered the previously included 31 studies from the 2009 version that included people with RA with biologic-failure as well as other RA subpopulations. The Cochrane Information Specialist conducted a search starting at the end date of the last search (for the 2009 version) and up to July 2015, for this 2015 update. We also searched trial registries at ClinicalTrials.gov and WHO trials register.

Data collection and analysis

Selection of reviews

Two teams of two abstractors each (JS/TC; SN/TC) reviewed the results of the search (titles and abstracts), and obtained the full text of articles identified as relevant.

Data extraction and management

Two teams of two abstractors each (SN/TC; JS/TC) independently extracted data from the trials of biologic or tofacitinib use in people with RA whose previous treatment with biologics had failed,

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using a predefined data extraction form created as a Microsoft Excel® spreadsheet (designed by JS) for the 2015 update. TC double-checked data for accuracy after the initial abstraction. We resolved disagreements by discussion with JS (or GW, as appropriate). We obtained additional information from the original RCTs where necessary, from the online supplementary materials or by contacting/emailing study authors.

We abstracted data for analyses only for the duration that participants were treated with biologic or the comparator that they were randomized to. We decided a priori not to analyze outcomes assessed/reported after the 'early escape' phase, where participants are provided active medication (biologic) even if they were previously in the placebo/comparator group, since these assessments are usually after two different exposures in the placebo/comparator group, and make it difficult for attribution of benefit or harm.

Assessment of methodological quality of included reviews

Two abstractors independently evaluated the risk of bias (JS/EG) of the included studies and the overall quality of the evidence (AM/JS). We combined these 'Risk of bias' data with corresponding data from the 2009 version for studies among biologic-experienced participants.

Risk of bias in included trials

Two abstractors (TC/JS) independently assessed risk of bias for each included trial using the Cochrane 'Risk of bias' tool based on the following criteria: random sequence generation, allocation concealment, presence of blinding (participants, personnel, and outcome assessors), incomplete outcome data, and selective outcome reporting (Higgins 2011). We assessed the risk of bias as recommended: 'low risk', 'high risk', or 'unclear risk' (either lack of information or uncertainty over the potential for bias). The review authors resolved any disagreements by discussion.

Quality of evidence

Two review authors (AM/JS) independently assessed the overall quality of the evidence for each outcome using the GRADE approach (Guyatt 2008). The GRADE approach improves reliability in comparison to intuitive judgments about the certainty of a body of evidence (Mustafa 2013). The GRADE system specifies four levels of quality of evidence.

1. High quality for randomized trials; or double-upgraded observational studies
2. Moderate quality for downgraded randomized trials; or upgraded observational studies
3. Low quality for double-downgraded randomized trials; or observational studies
4. Very low quality for triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports

Randomized trial evidence could be downgraded by one or two levels depending on the presence of five factors.

1. Serious (-1) or very serious (-2) limitation to study quality
2. Important inconsistency (-1)
3. Some (-1) or major (-2) uncertainty about directness
4. Imprecise or sparse data (-1)

5. High probability of reporting bias (-1)

Data synthesis

Statistical analyses

We performed the standard and NMA analyses including important factors such as the route of biologic (intravenous versus subcutaneous), dose (low dose (LD) versus standard dose (SD) versus high dose (HD)) and concomitant MTX/DMARD, for the 2015 update. We also performed pre-specified analyses for subgroups by trial and RA disease duration, since they might contribute to differences in benefits and harms of biologics. We considered P values less than 0.05 and 95% CIs (for standard meta-analyses) or credible intervals (CrI; for network meta-analyses) that did not include 1 to be statistically significant.

The standard meta-analysis (direct comparisons) determined the effectiveness of treatments directly compared to each other and was performed using Review Manager 5 (RevMan 5) (RevMan 2014). In order to handle rare events in direct comparison meta-analyses, we used Peto's odds ratios as the effect measure. For other outcomes, we used odds ratio (OR) or mean difference (MD) as effect measures. We used the I^2 statistic for quantifying heterogeneity of the results in individual studies (Higgins 2003), since heterogeneity is a common issue encountered while performing meta-analyses (Higgins 2002; Thompson 1999). This statistic combines the Chi^2 statistic and the number of studies contributing to each summary estimate in the figure. In all the forest plots presenting effect measure data per treatment, we applied the random-effects model as the default option (Dersimonian 2007) for illustrative purposes. We estimated the number needed to treat for an additional beneficial outcome (NNTB) and harmful outcome (NNTH), with 95% CIs on the basis of the derived OR comparing treatment to control and considering the overall event rate in the placebo group as a proxy for the community baseline event rate. This method enables direct translation into clinical practice (Osiri 2003), using Visual Rx with the overall (pooled) number of responders within the available studies as proxy for the expected rate of responders in a given RA population (Cates 2009).

We conducted a network meta analysis (NMA) based on a Bayesian mixed treatment comparison (MTC) approach, using the WinBUGS statistical software for the Bayesian analysis (MRC Biostatistics Unit, Cambridge, UK) (Spiegelhalter 2003). We performed Markov Chain Monte Carlo (MCMC) simulation approach with at least 5000 or more iterations (as needed) to derive the corresponding 95% CrIs. We used informative priors for the variance parameters (Turner 2012). Where considered more suitable, we used vague priors for basic parameters. Assessment of model fit for the NMA was based on deviance information criterion (DIC) and comparison of residual deviance (Spiegelhalter 2003). We assessed trace plots and the Brooks-Gelman-Rubin statistic to ensure that convergence was reached (Spiegelhalter 2003). We applied the continuity correction for zero event cells to make non-zero cells where needed. In order to assess inconsistency (conflict between direct and indirect evidence (Wells 2009)), we compared deviance and deviance information criteria (DIC) statistics in fitted consistency and inconsistency models (Dias 2011) and examined the inconsistency plot. We chose between the random-effects model and the fixed-effect model based on the assessment of the DIC and comparison of residual deviance to number of unconstrained data points. We used OR as the effect measure for dichotomous outcomes, that is, the number

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of participants achieving ACR50, remission, serious adverse events, and withdrawals due to adverse events; and MD for continuous outcomes such as HAQ and radiographic progression. For cancer data, we anticipated that events would be rare (Bradburn 2007; Sweeting 2004). In order to handle these expected sparse data, we applied an empirical Bayes (treatment arm-based) approach (Salanti 2008). AK and AH performed data analyses under the supervision of GW.

Sub-group analyses/planned comparisons

We compared biologics or tofacitinib to comparators and to each other with regards to benefits and harms as the main analysis using the NMA, when feasible.

In addition, we specified that we would perform the following subgroup analyses using the NMA, when feasible, that is, there were five or more trials in each of the subcategories.

1. Trial duration: short duration (six months or less), intermediate duration (between six and 12 months) or long duration (more than 12 months)
2. RA disease duration, as previously defined in two studies (Barlow 1999; Boers 2001): early RA (mean/median duration of less than two years) (Boers 2001), established RA (mean/median duration two to 10 years) or late RA (mean/median duration more than 10 years) (Barlow 1999)

In addition, we specified a priori that we would calculate overall ORs for the following using the standard meta-analysis or NMA, when feasible.

1. Overall biologic versus placebo/control (standard meta-analysis)
2. TNF inhibitor biologics (etanercept (ETN), adalimumab (ADA), certolizumab pegol (CERT), golimumab (GOLI), infliximab (INF)) versus non-TNF biologics (abatacept (ABA), rituximab (RITUX), tocilizumab (TOCI)) versus anakinra (ANA) versus tofacitinib (TOFA) (NMA)
3. Medications targeting TNF receptor ETN versus monoclonal antibodies against TNF (ADA, CERT, GOLI, INF) versus non-TNF (ABA, RITUX, TOCI) versus ANA versus TOFA (NMA)
4. High-dose (HD) versus standard dose (SD) versus low-dose (LD) biologic versus TOFA. We defined the standard doses of biologics as in the 2009 version and expanded to include definitions

for the newer biologics and routes since the 2009 version and tofacitinib, as follows (NMA; Appendix 1):

a. abatacept IV: every four weeks intravenously at 500 mg dose in people weighing less than 60 kg, 750 mg in people weighing 60 kg to 100 kg and 1000 mg in people weighing more than 100 kg, after the initial dosing regimen of baseline, two- and four-week infusions;
b. abatacept SQ: 125 mg subcutaneous weekly;adalimumab: 40 mg subcutaneous every two weeks;
c. anakinra: 100 mg subcutaneous every day;certolizumab pegol: 400 mg initially and at weeks two and four, followed by 200 mg every other week (for maintenance dosing, 400 mg every four weeks can be considered);
d. etanercept: 25 mg subcutaneous twice weekly or 50 mg subcutaneous once weekly;
e. golimumab: 50 mg administered by subcutaneous injection once a month;
f. infliximab: 3 mg/kg intravenous (IV) every eight weeks after initial dosing at zero, two and six weeks;
g. rituximab: two 1000 mg IV doses two weeks apart;
h. tocilizumab IV: starting dose is 4 mg per kg every four weeks followed by an increase to 8 mg per kg every four weeks based on clinical response;
i. tocilizumab SC: 162 mg administered subcutaneously every other week, followed an increase to every week based on clinical response for people weighing less than 100 kg, and 162 mg administered subcutaneously every week for people weighing 100 kg or more; and tofacitinib: 5 mg orally twice a day or 10 mg orally once daily.

RESULTS

Description of included reviews

NOTE: this update uses individual studies, not reviews, for the basis of all analyses

Figure 1 shows the overall study selection process that included the studies identified for inclusion in the 2015 update. With the 2015 update, we identified a total of 12 studies from 8771 titles (including three of the 31 RCTs from the Cochrane reviews in the original 2009 version), and all 12 studies with 3364 participants provided data for analyses (Table 1). Of these, 67% (8/12) studies were six months or less in duration, 17% (2/12) were six months' to 12 months' duration, and 17% (2/12) were longer than 12 months.

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Figure 1.   Study flow diagram
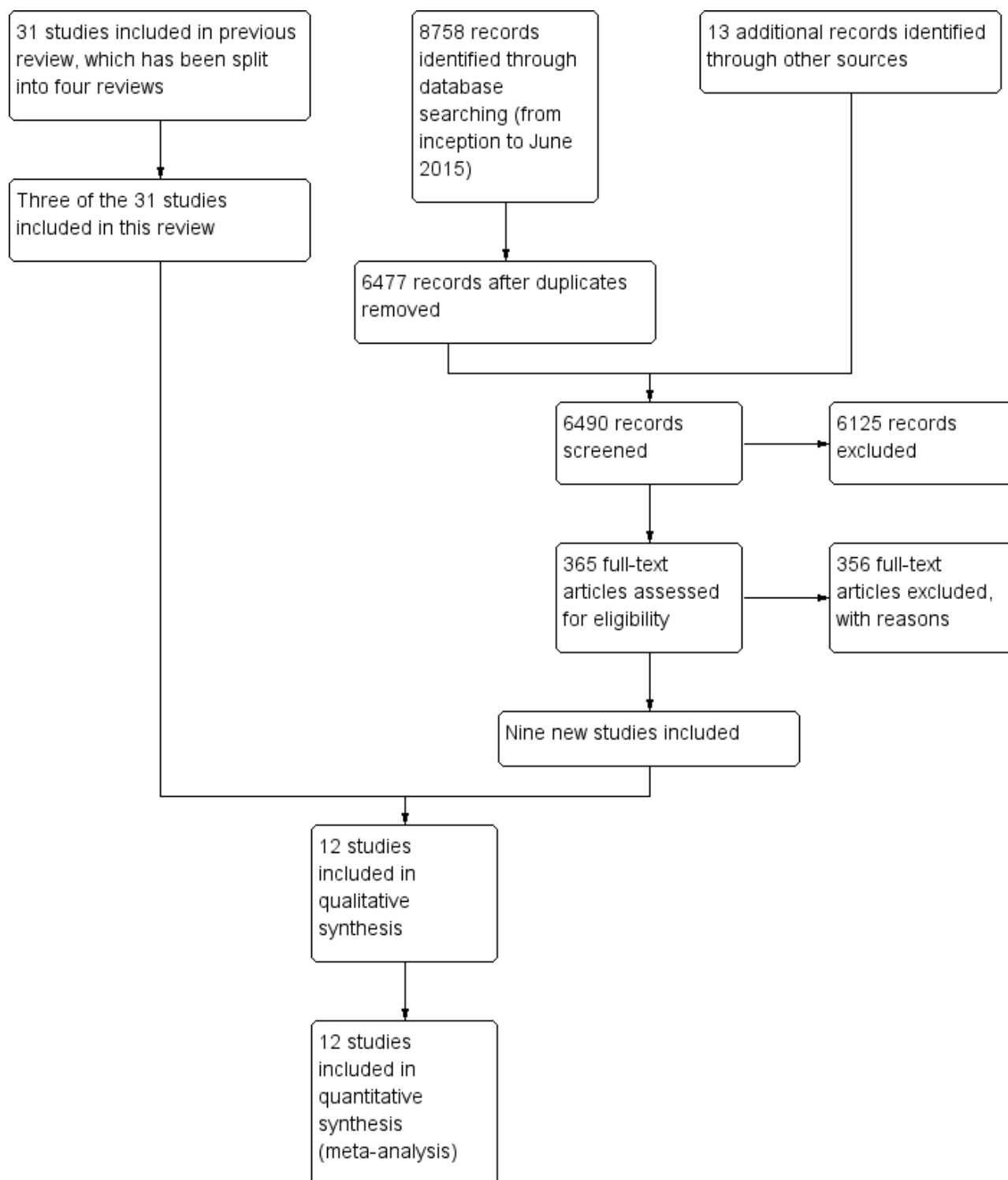
The comparators were as follows: placebo in 25% (3/12), MTX/DMARD in 50% (6/12), and another biologic in 25% (3/11). In two of the three studies with a placebo comparator, participants continued their background DMARD (most often MTX) use; in the third study of multiple doses of CTLA-4Ig (abatacept) and LEA29Y, participants had been unsuccessfully treated with at least one traditional DMARD or etanercept (the study started before the approval of infliximab), and both DMARD and etanercept were discontinued 28 days prior to starting the study. We have provided reasons for exclusion of studies that were reviewed as full text in Table 2. One study provided data for tofacitinib. Ongoing trials from the WHO trials register and Clinicaltrials.gov are listed in Appendix 2.

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Treatment with one or more TNF-biologic had failed, due to inadequate response or intolerance to TNF-biologic in four studies (Bingham 2015; Emery 2008a; Schiff 2014b; Smolen 2009) or inadequate response to TNF-biologic only in eight studies (Burmester 2013; Cohen 2006; Furst 2007; Genovese 2005; Keystone 2008; Moreland 2002; Weinblatt 2007a; Weinblatt 2008).

Methodological quality of included reviews

Risk of bias of included trials in the 2015 update

Detailed 'Risk of bias' assessments for each trial including the reasons for each judgment are available on the Cochrane Musculoskeletal website (Risk of bias A and Risk of bias B).

Random sequence generation (selection bias)

All trials were described as randomized, however, only four out of 12 (33%) reported adequate sequence generation and we assessed them as low risk, while eight (67%) did not describe the method used and we assessed them as unclear risk. We did not assess any studies as high risk of bias for random sequence generation.

Allocation concealment (selection bias)

We assessed allocation concealment as low risk in four (33%) trials and unclear in eight (67%) trials. We did not assess any studies as high risk of bias for allocation concealment.

Blinding of participants and personnel (performance and detection bias)

We judged a total of four (33%) trials at low risk of performance bias, and six (50%) at unclear risk of bias. In two (17%) trials, participants were not blinded and we judged these trials at high risk of performance bias.

We assessed low risk of detection bias in three (25%) trials, high risk of detection bias in two (17%) and unclear risk in seven (58%) trials.

Incomplete outcome data (attrition bias)

We judged most trials (eight out of 12; 67%) at high risk of attrition bias because more than 20% of participants dropped out. Three (25%) trials had low risk of attrition bias and one (8%) trial was unclear risk.

Selective reporting (reporting bias)

We judged 11 (92%) trials as unclear risk since the study protocols were not available and we did not have enough information in the study report to assess selective reporting. We judged one (8%) trial at low risk of selective reporting bias. We judged 11 (92%) trials as unclear risk since the study protocols were not available.

Other potential sources of bias

We assessed major baseline imbalance and all studies (100%) trials had low risk of bias.

Effect of interventions

We followed the following principles while describing results to keep this review as comprehensive as possible:

1. We first present the overall odds ratio (OR) for the entire group, followed by pre-specified comparisons (e.g. TNF vs. non-TNF vs. TOFA), followed by the main analyses and then the pre-specified subgroup analyses, where data were available.

2. In the overall OR analyses, only the last set of ORs compare the biologic by dose; other analyses prior to the dose analysis include all doses and provide comparison by a different characteristic of interest (e.g. the type of biologic).

3. In the 'Main analyses' section (that follows overall OR section), when not specified, the biologic or TOFA is in standard dose. We specify high-dose (HD) and low-dose (LD) in every instance.

4. For biologics that are approved for only one route of administration (i.e. intravenous or subcutaneous), we do not specify the route. Mention of the drug without the route implies the only approved route for the drug: subcutaneous for adalimumab, anakinra, certolizumab pegol, etanercept and golimumab; intravenous (IV) for infliximab, and rituximab; and oral for tofacitinib. Since only two biologics are approved for both intravenous and subcutaneous use (tocilizumab and abatacept), we specify these routes when describing results for these medications. Additionally some biologics have data on routes of administration that were tested in Phase II/III trials, but not approved for use. Our review includes these data.

5. Due to our attempt to keep the narrative short, we discuss only significant or clinically meaningful results in the text. The tables represent the entire comparison, for interested readers.

6. For each outcome, we present the quality of evidence in the 'Summary of findings' table, Abstract and in the text below. The quality of the evidence takes into account risk of bias, inconsistency, indirectness, imprecision and reporting bias.

'Summary of findings' table

The 'Summary of findings' table for biologic-experienced participants (Table 3) presents both the direct estimates of biologic or tofacitinib versus comparator (MTX/DMARD or placebo) and the estimates from the NMA with a rating of the quality of evidence for direct as well as NMA estimates. For each estimate we have provided absolute risk difference as well as relative difference (converted from OR in the NMA to risk ratio (RR) in the 'Summary of findings' table for ease of interpretation for clinicians).

Compared to placebo, biologic monotherapy was associated with clinically meaningful and statistically significant improvement for ACR50 and RA disease remission (with moderate-quality evidence, downgraded for imprecision due to smaller number of events). Results for withdrawals due to adverse events and serious adverse events were inconclusive with low-quality evidence. There were no studies available with placebo comparators for analysis for function, cancer, or radiographic progression. There were no studies comparing tofacitinib monotherapy to placebo.

When compared to MTX/DMARD, biologic + MTX and tofacitinib + MTX use were each associated with clinically meaningful and statistically significant improvement for three important benefit outcomes, ACR50 and function as measured by the HAQ (with high-quality evidence) [a "negative" sign for HAQ indicates improvement in function; lower HAQ values indicate better function], and RA disease remission (with moderate-quality evidence, downgraded for imprecision due to smaller number of events). For two of these outcomes (ACR50 and RA disease remission), direct estimates were consistent with the NMA estimates for both overall and subgroup (TNF + MTX/DMARD, non-TNF + MTX/DMARD, and tofacitinib + MTX/DMARD) analyses. Tofacitinib + MTX use was not associated with

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any clinically meaningful and statistically significant improvement in RA disease remission, with moderate-quality evidence.

There were no studies for radiographic progression for biologic + MTX or tofacitinib + MTX. Results for withdrawals due to adverse events, and serious adverse events were inconclusive with moderate- and low-quality evidence for biologic + MTX and tofacitinib + MTX and for all biologic sub-categories (TNF- or non-TNF biologic). Results for cancer were inconclusive with moderate and low quality evidence for biologic + MTX and all biologic categories, where data were available. No data were available for cancer for tofacitinib + MTX. Most NMA estimates were consistent with the direct estimates discussed in the section above, with minimal differences in estimates and with a similar or slightly lower quality of evidence (Table 3).

Number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH)

Comparing biologic monotherapy to placebo, NNTBs for ACR50 and RA disease remission, were 8 and 11, respectively; no data were available for HAQ. For ACR50, HAQ and remission, NNTBs for biologic + MTX overall when compared to MTX/DMARD were 7, 5 and 17, respectively.

No NNTBs were available for TNF or non-TNF biologic subgroups for biologic monotherapy to placebo comparisons. NNTB ranged from 5 to 9 for ACR50 among TNF + MTX/DMARD and non-TNF + MTX/DMARD biologic subgroups and tofacitinib + MTX. NNTB ranged from 4 to 5 for HAQ improvement for overall biologic + MTX or tofacitinib + MTX compared to MTX/DMARD. For remission, NNTB ranged from 9 to 18 in the TNF + MTX/DMARD and non-TNF + MTX/DMARD biologic subgroups. There were no studies for radiographic progression.

For the harms outcomes, no outcomes provided significant results for the calculation of an NNTH.

Main analysis: comparison of the nine biologics or tofacitinib with regard to benefit and safety

Primary/major benefit outcome: ACR50

Ten studies with 2774 participants reported ACR50. Of these, four studies included at least one arm with participants on a biologic with concomitant MTX/DMARD (most often MTX) and three studies included only biologic monotherapy (no concomitant MTX/DMARD therapy). An example of network diagram for ACR50 for biologic-experienced participants is shown in Figure 2.

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Figure 2. Network diagram for ACR50 in people with RA who are biologic-experienced
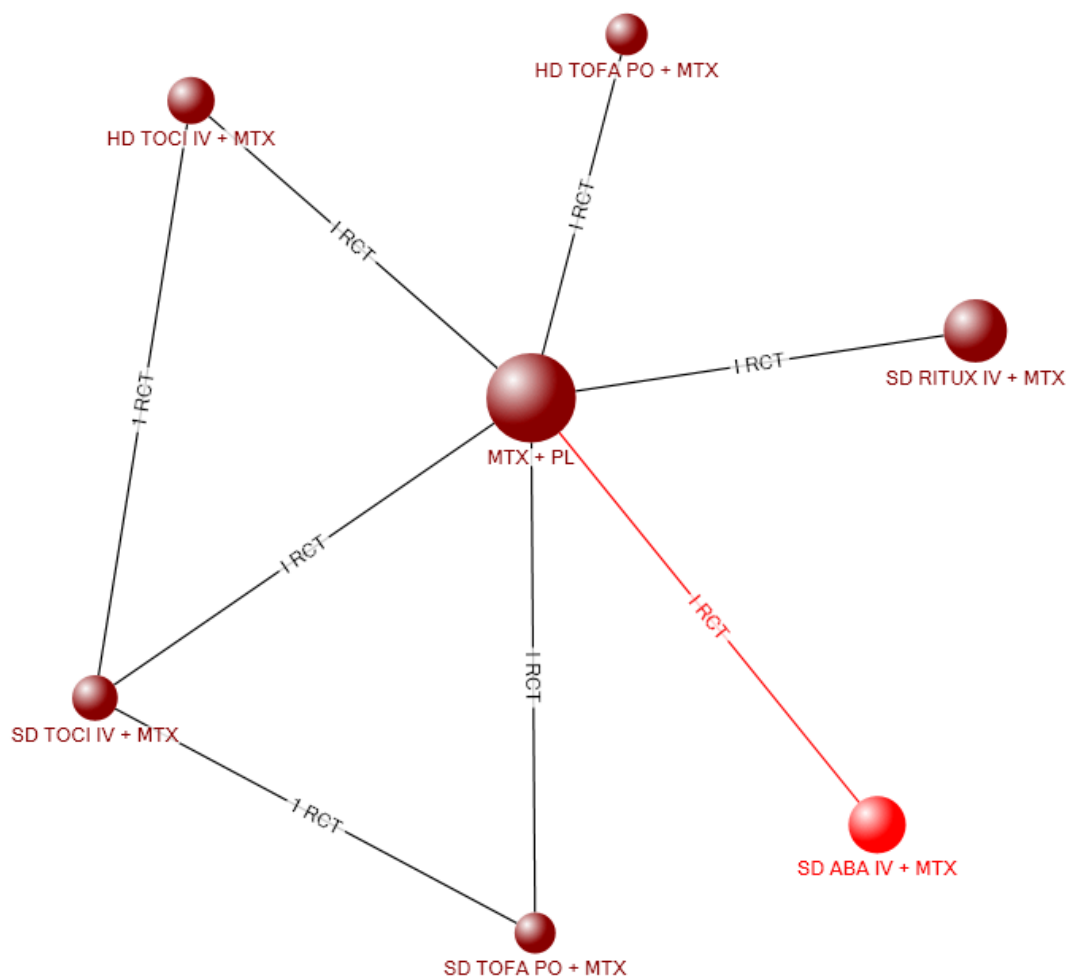
Overall odds using standard meta-analyses

The figures (Figure 3; Figure 4) show the overall odds of ACR50 with biologic monotherapy or in combination with MTX/DMARD versus comparator. Biologics were associated with the following odds of ACR50 versus the respective comparator.

Figure 3. ACR50: biologic monotherapy vs. placebo

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Figure 4. ACR50: biologic with MTX vs. MTX/DMARD

1. Compared to placebo, biologic monotherapy (3 studies), OR 4.84 (95% CI 2.22 to 10.55), I^2 of 0% indicating no heterogeneity (Figure 3) and a clinically meaningful and statistically significant improvement. Biologic with concomitant MTX: no studies were available for analysis.
2. Compared to MTX/DMARD, biologic with concomitant MTX (3 studies), OR 4.93 (95% CI 3.16 to 7.70), I^2 of 10% indicating mild heterogeneity (Figure 4). Biologic monotherapy: no studies were available for analysis.

Odds by biologic type and dose using NMA

The overall rates of ACR50 by the type of biologic and the dose, using the NMA, were as follows.

1. Type of biologic (2267 participants, 5 studies)
   a. On background MTX: compared to non-TNF biologic, TNF biologic was not associated with any statistically significant difference in ACR50, OR 0.51 (95% CrI 0.18 to 1.54); similar non-statistically significant results were seen when comparing tofacitinib to non-TNF biologic, OR 0.65 (95% CrI 0.23 to 1.86) or TNF biologic, OR 1.26 (95% CrI 0.36 to 4.40). (Table 4)
   b. Not on background MTX: no studies were available for analysis.
2. Type of biologic, receptor versus antibody
   a. On background MTX: since there were no studies available for etanercept, the results were the same as those for 1a above.
   b. Not on background MTX: no studies were available for analysis.
3. By dose
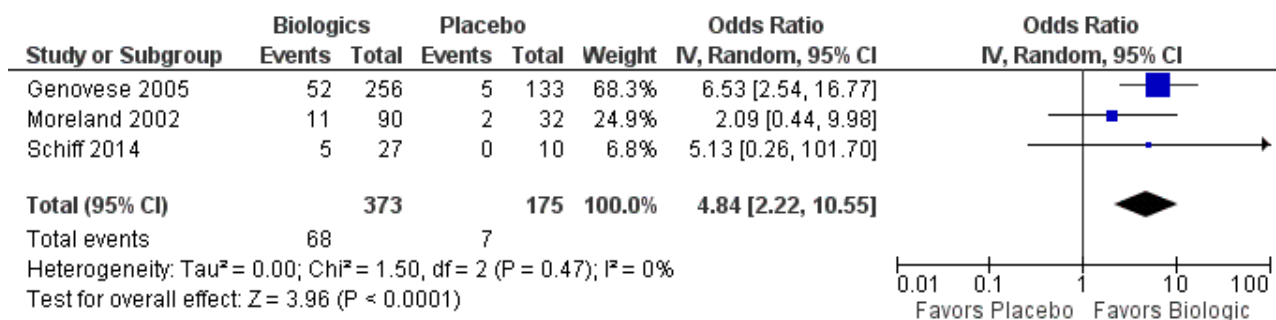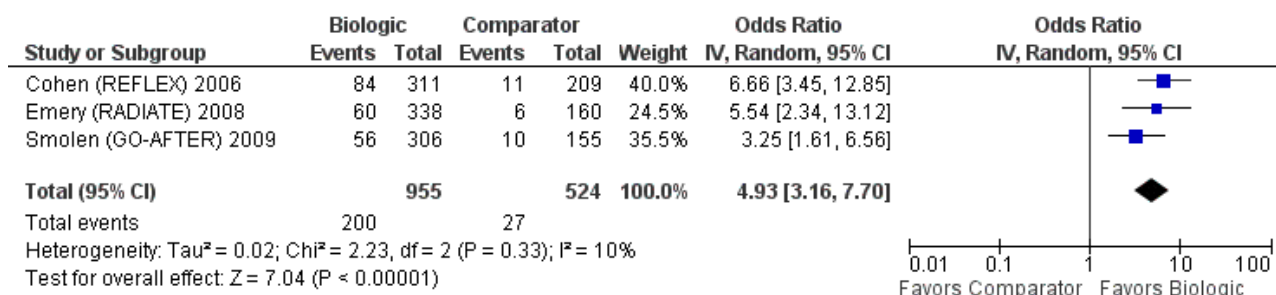
a. On background MTX (1868 participants, 4 studies): compared to standard dose biologic, HD biologic was associated with no statistically significant differences, OR 1.47 (95% CrI 0.84 to 2.54). (Table 5)
b. Not on background MTX (359 participants, 3 studies): compared to standard dose biologic, HD biologic was associated with no statistically significant differences, OR 1.24 (95% CrI 0.49 to 3.32). (Table 6).

Main analyses using NMA

There were not enough data from the included studies to perform NMA.

Subgroup analyses by RA disease duration (early versus established versus late RA)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

There were not enough data to perform NMA.

Primary/major efficacy outcome: HAQ

Five studies with 1701 participants reported data on function as measured by HAQ (0 to 3 scale; higher means worse function). Of these, three studies included at least one arm with participants on a biologic with concomitant MTX/DMARD. The other two studies had only biologic monotherapy (no concomitant MTX/DMARD therapy) and were compared to another biologic.

Overall MD using standard meta-analyses

Figure 5 shows the results of the comparison of biologic in combination with MTX/DMARD versus MTX/DMARD comparator.

Figure 5. HAQ: biologic with MTX vs. MTX/DMARD
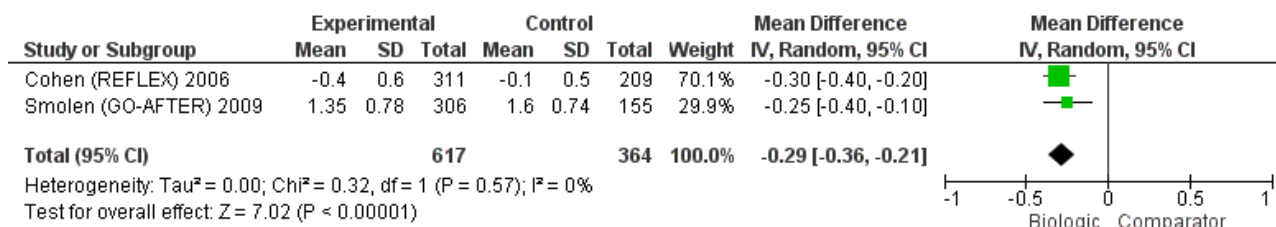
1. Compared to placebo: no studies available for analysis.
2. Compared to MTX/DMARD, biologic with concomitant MTX (2 studies): mean difference in HAQ improvement of -0.29

(95% CI -0.36 to -0.21), I^2 of 0%, indicating no heterogeneity, which may be clinically meaningful [a "negative" sign indicates

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improvement in function; lower values indicate better function]. Biologic monotherapy: no studies available for analysis.

ORs by biologic type and dose using NMA

The overall MD in HAQ scores by the type of biologic and the dose, using the NMA, were as follows.

1. Type of biologic (1358 patients, 3 studies)
   a. On background MTX: compared to non-TNF biologic, TNF biologic did not show a statistically significant mean difference in HAQ score, MD -0.12 (95% CrI -8.96 to 8.75) [a "negative" sign indicates improvement in function; lower values indicate better function]; similar non-statistically significant results were seen when comparing tofacitinib to non-TNF, MD -0.02 (95% CrI -8.82 to 8.80) or TNF biologic, MD 0.11 (95% CrI -8.83 to 8.97). (Table 7)
   b. Not on background MTX: No studies were available for analysis.
2. Type of biologic, receptor versus antibody (1358 participants, 3 studies)
   a. On background MTX: since there were no studies available for etanercept, the results were the same as those for 1a above.
   b. Not on background MTX: No studies were available for analysis.
3. By Dose
   a. On background MTX: no studies were available for analysis.

b. Not on background MTX: no studies were available for analysis.

Main analyses using NMA

There were not enough data to perform NMA.

Subgroup analyses by RA disease duration (early versus established versus late RA)

There were not enough data to perform NMA.

**Subgroup analyses by trial duration**

There were not enough data to perform NMA.

Primary/major efficacy outcome: remission

Six studies with 1974 participants reported data on remission. Of these, three studies included at least one arm with participants on a biologic with concomitant MTX/DMARD and three studies had no concomitant MTX/DMARD therapy (one compared to placebo and two compared to another biologic).

Overall odds using standard meta-analyses

The figure below (Figure 6) shows the overall odds of RA remission with biologic in combination with MTX/DMARD versus MTX/DMARD comparator. Biologics were associated with the following odds of RA remission versus the respective comparator.

Figure 6. RA remission: biologic with MTX vs. MTX/DMARD
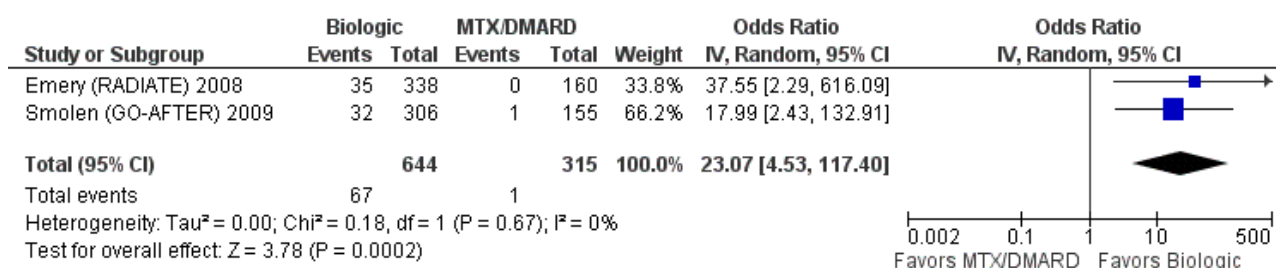
1. Compared to placebo, biologic monotherapy, there was one study, OR 14.92 (95% CI 4.53 to 117.40), which is clinically meaningful at 9% improvement (95% CI 5% to 13%) (data not shown in Figure 6); biologic with concomitant MTX no studies were available for analysis.
2. Compared to MTX/DMARD, biologic with concomitant MTX (2 studies), OR 23.07 (95% CI 4.53 to 117.40), I2 of 0%, indicating no heterogeneity (Figure 6); biologic monotherapy, no data were available.

Odds by biologic type and dose using NMA

The overall rates of remission by the type of biologic and the dose, using the NMA, were as follows.

1. Type of biologic (1348 participants, 3 studies)
   a. On background MTX: compared to non-TNF biologic, TNF biologic was not associated with any statistically significant or clinically meaningful difference in the odds of remission, OR 0.75 (95% CrI 0.04 to 26.4). (Table 8)
   b. Not on background MTX: There were no data to perform this analysis

2. Type of biologic, TNF receptor versus antibody (1348 patients, 3 studies)
   a. On background MTX: since there were no studies available for etanercept, the results were the same as those for 1a above.
   b. Not on background MTX: there were no data to perform this analysis.
3. By dose (1348 patients, 3 studies)
   a. On background MTX: compared to standard dose biologic, HD biologic was associated with statistically significantly higher rates of remission, OR 3.62 (95% CrI 1.19 to 12.87). (Table 9)
   b. Not on background MTX: there were no data to perform this analysis.

Main analyses using NMA

There were not enough data from the included studies to perform NMA.

Subgroup analyses by RA disease duration (early versus established versus late RA)

There were not enough data to perform NMA.

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Subgroup analyses by trial duration

There were not enough data to perform NMA.

Primary/major efficacy outcome: radiographic progression

No studies were available for analysis.

Primary/major safety outcome: withdrawals due to adverse events

Seven studies with 1584 participants reported withdrawals due to adverse events. Of these, four studies included at least one arm with participants on a biologic with concomitant MTX and three studies had no concomitant MTX/DMARD therapy (one with other biologic comparators and two compared to placebo).

Overall ORs using standard meta-analyses

The figures below (Figure 7; Figure 8) show the overall OR of withdrawals due to adverse events with biologic versus comparator. Biologics were associated with the following odds of withdrawals due to adverse events versus the respective comparator.

Figure 7. Withdrawals due to adverse events: biologic monotherapy vs. placebo
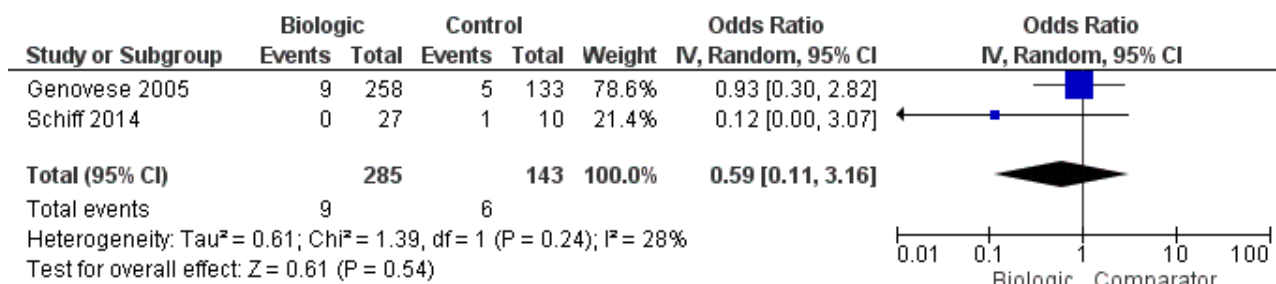
Figure 8. Withdrawals due to adverse events: biologic with MTX vs. MTX/DMARD
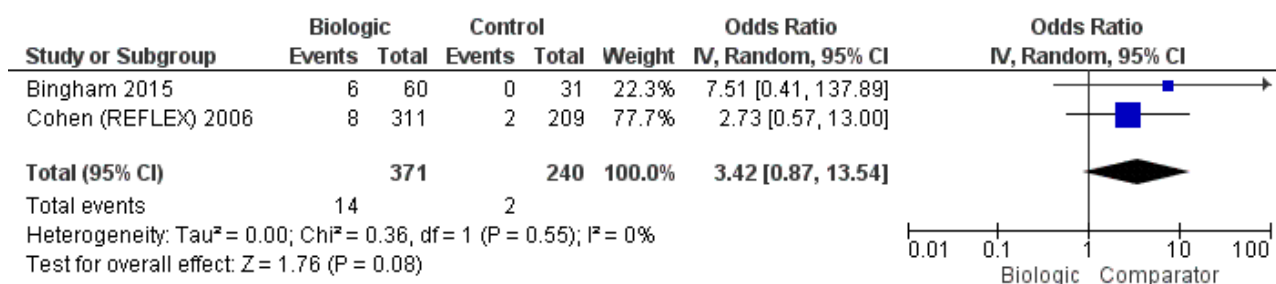
1. Compared to placebo, biologic monotherapy (2 studies), OR 0.59 (95% CI 0.11 to 3.16), I^2 of 28% indicating mild heterogeneity (Figure 7); biologic with concomitant MTX, no data were available.
2. Compared to MTX/DMARD, biologic with concomitant MTX (2 studies), OR 3.42 (95% CI 0.87 to 13.54), I^2 of 0% indicating no heterogeneity (Figure 8); biologic monotherapy, no data were available.

ORs by biologic type and dose using NMA

The overall withdrawals due to adverse events by the type of biologic and the dose, using the NMA, were as follows.

1. Type of biologic (1401 participants, 4 studies)
   a. On concomitant MTX: compared to non-TNF biologic, tofacitinib was not associated with any statistically significant or clinically meaningful difference in the odds of withdrawals due to adverse events, OR 0.50 (95% CrI 0.09 to 2.55). (Table 10)
   b. Not on concomitant MTX: no analyses could be performed.

2. Type of biologic, TNF receptor versus antibody (1401 participants, 4 studies)
   a. On concomitant MTX: since there were no studies available for etanercept, the results were the same as those for 1a above.
   b. Not on concomitant MTX: no meaningful analysis could be performed due to lack of data.
3. By dose (1401 participants, 4 studies)
   a. On concomitant MTX: no meaningful analysis could be performed due to lack of data.
   b. Not on concomitant MTX: no meaningful analysis could be performed due to lack of data.

Main analyses using NMA

There were not enough data from the included studies to perform NMA.

Subgroup analyses by RA disease duration (early versus established versus late RA)

There were not enough data to perform NMA.

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Subgroup analyses by trial duration

There were not enough data to perform NMA.

Primary/major safety outcome- serious adverse events

Nine studies with 2245 participants reported serious adverse events (SAEs). Of these, five studies included at least one arm with participants on a biologic with concomitant MTX/DMARD (most often MTX) and four studies had no concomitant MTX/DMARD therapy (two studies had other biologic comparators and two were compared to placebo).

Overall ORs using standard meta-analyses

The figure (Figure 9) below shows the overall OR of serious adverse events with biologic in combination with MTX/DMARD versus MTX/DMARD comparator. Biologics were associated with the following OR of SAE versus the respective comparator:
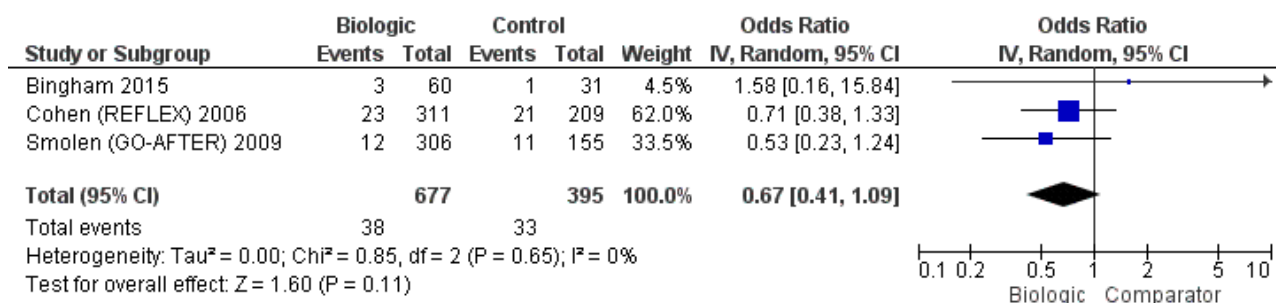
Figure 9. Serious adverse events: biologic with MTX vs. MTX/DMARD

1. Compared to placebo, biologic monotherapy, there was one study that provided data, with an OR of 0.92 (95% CI 0.47 to 1.80) (data not shown in Figure 9); biologic with concomitant MTX, no data were available.
2. Compared to MTX/DMARD, biologic with concomitant MTX/DMARD, OR of 0.67 (95% CI 0.41 to 1.09), I^2 of 0%, indicating no heterogeneity (Figure 9); biologic monotherapy, no data were available.

ORs by biologic type and dose using NMA

The overall SAEs by the type of biologic and the dose, using the NMA, were as follows.

1. Type of biologic (1862 participants, 5 studies)
   a. In participants receiving concomitant MTX, compared to non-TNF biologics the odds of SAEs were not statistically significantly different with TNF biologics, OR 0.64 (95% CrI 0.19 to 2.13). Likewise, the odds of SAEs were not statistically significantly different when comparing tofacitinib to non-TNF biologics, OR 0.36 (95% CrI 0.07 to 1.70) or TNF biologic, OR 0.56 (95% CrI 0.09 to 3.37). (Table 11)
   b. In participants not receiving concomitant MTX, there were no data for comparisons.
2. Type of biologic, TNF receptor versus antibody (1862 participants, 5 studies)
   a. In participants receiving concomitant MTX, results same as above in 1a, since there were no etanercept trials.
   b. In participants not receiving concomitant MTX, there were no data for comparisons.
3. By dose (1463 participants, 4 studies):
   a. In participants receiving concomitant MTX, the odds of SAEs were not statistically significantly different with HD biologic compared to SD biologic, OR 0.60 (95% CrI 0.20 to 1.65). (Table 12)
   b. In participants not receiving concomitant MTX, there were no data for comparisons.

Main analyses using NMA

There were not enough data from the included studies to perform NMA.

Subgroup analyses by RA disease duration (early versus established versus late RA)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

There were not enough data to perform NMA.

Primary/major safety outcome: cancer

Two studies with 552 participants reported a cancer outcome. Of these, both studies included at least one arm with participants on a biologic with concomitant MTX/DMARD. One study contained no events of cancer for either the biologic or comparator arms.

Overall Peto odds ratios using standard meta-analyses

Biologics were associated with the following OR of cancer versus the respective comparator:

1. Compared to placebo, there were no studies that provided data.
2. Compared to MTX/DMARD, biologic with concomitant MTX, one study provided data to calculate odds of cancer which were not statistically significant, OR 4.53 (95% CI 0.07 to 285.5); biologic monotherapy, no data were available.

OR by biologic type and dose using NMA

The overall rate of cancer by the type of biologic and the dose could not be calculated due to the low number of studies.

Main analyses using NMA

There were not enough data from the included studies to perform NMA.

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Subgroup analyses by RA disease duration (early versus established versus late RA)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

There were not enough data to perform NMA.

Summary of safety warnings from regulatory agencies

Evidence from RCTs is limited in informing patients and physicians regarding uncommon or rare adverse events. Appendix 3 summarizes the warnings from the FDA, EMA and Health Canada, the regulatory agencies in the USA, Europe and Canada, respectively.

DISCUSSION

Summary of main results

Biologic or tofacitinib monotherapy compared to placebo

ACR50

Biologic monotherapy showed a clinically meaningful and statistically significant increased rate of ACR50 compared to placebo with a RR 4.10 (95% CI 1.97 to 8.55; moderate-quality evidence) and absolute benefit of 14% (95% CI 6% to 21%) in standard meta-analyses.

Function assessed by HAQ

No studies were available for analysis of HAQ scores for biologic monotherapy versus placebo comparison.

Remission

There was one study available for biologic monotherapy compared to placebo, showing a clinically meaningful and statistically significant RR of 13.51 (95% CI 1.85 to 98.45) and absolute benefit of 9% (95% CI 5% to 13%) for improved RA remission rate (moderate-quality evidence) in standard meta-analyses.

Radiographic Progression

No studies were available for analysis.

Withdrawals due to adverse events

Based on low-quality evidence, results were inconclusive in standard meta-analyses for withdrawals due to adverse events with biologic monotherapy compared to placebo, with wide confidence intervals encompassing the null effect and evidence of an important increase.

Serious adverse events (SAEs)

Based on low-quality evidence, the results were inconclusive in standard meta-analyses for serious adverse events with biologic monotherapy compared to placebo, with wide confidence intervals encompassing the null effect and evidence of an important increase in serious adverse events.

Cancer

No studies were available for analysis of cancer outcome for biologic monotherapy versus placebo.

Biologic + MTX or tofacitinib + MTX compared to MTX/DMARD

ACR50

There was high-quality evidence that biologic + MTX use showed a clinically meaningful and statistically significant increased rate of ACR50 compared to the comparator (MTX/DMARD) with an RR of 4.07 (95% CI 2.76 to 5.99) and absolute benefit of 16% (95% CI 10% to 21%) in standard meta-analyses. Based on moderate-quality evidence, subgroups of TNF biologics and non-TNF biologics as well as tofacitinib (all in combinations with MTX) also showed statistically significant and clinically meaningful increased ACR50 rates versus comparator (MTX/DMARD) with RRs ranging from 2.84 to 4.99, absolute benefit ranging 12% to 19%. Similar results were seen in NMA for TNF biologic + MTX, non-TNF biologic + MTX and tofacitinib + MTX compared to MTX, based on moderate-quality evidence.

When comparing type of biologics using the NMA, TNF biologics (and monoclonal antibody TNF specifically), non-TNF biologics, and tofacitinib were not statistically or clinically different in ACR50 rates when compared to each other. There were also no statistically significant differences in ACR50 rates by the dose of the biologic.

Function assessed by HAQ

Based on high-quality evidence, compared to MTX/DMARD, biologics + MTX showed a clinically meaningful and statistically significant improvement in function assessed on HAQ score of 0 to 3, with a mean improvement of 0.29 (95% CI 0.21 to 0.36) and absolute improvement of 10% (7% to 12%) in standard meta-analyses [a "negative" sign indicates improvement in function; lower values indicate better function]. These mean improvements remained significant, with mean differences ranging from 0.25 to 0.37 and absolute improvement ranging from 8% to 12%, when comparing subgroups of TNF biologics and non-TNF biologics as well as tofacitinib (all in combination with MTX) to the comparator (MTX/DMARD). These results were not statistically significant but seemed clinically meaningful for TNF biologic + MTX, non-TNF biologic + MTX and tofacitinib + MTX compared to MTX in the NMA, with similar proportions and differences, based on low-quality evidence.

When comparing type of biologics using the NMA, TNF biologics, non-TNF biologics, and tofacitinib did not differ statistically significantly or clinically meaningfully from each other. There were not enough studies available to assess differences by dose using the NMA.

Remission

Biologic + MTX was associated with a clinically meaningful and statistically significant higher remission rate compared to the comparator (MTX/DMARD), with a RR of 20.73 (95% CI 4.13 to 104.16) and absolute benefit of 10% (95% CI 8% to 13%) (moderate-quality evidence) in standard meta-analyses. The subgroups of TNF biologics and non-TNF biologics (in combination with MTX) also showed similar, statistically significantly and clinically meaningfully higher remission rates versus comparator (MTX/DMARD), while comparison of tofacitinib to comparator was not statistically significant or clinically meaningful. Similar results for TNF biologic + MTX and non-TNF biologic + MTX compared to MTX were seen in NMA, also with moderate-quality evidence.

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Using the NMA, we found that the TNF biologic did not show a clinically meaningful difference or differ statistically significantly from non-TNF biologic with regards to the remission rates. HD biologic (+ MTX) was associated with significant and clinically meaningful higher rates of remission compared to SD biologic (+ MTX), the OR was 3.62 (95% CI 1.19 to 12.87).

Radiographic Progression

No studies were available for analysis.

Withdrawals due to adverse events

Based on low-quality evidence, results were inconclusive in standard meta-analyses for withdrawals due to adverse events for biologic + MTX therapy or tofacitinib + MTX compared to MTX/DMARD, with wide confidence intervals encompassing the null effect and evidence of an important increase. Based on low-quality evidence, results were also inconclusive for non-TNF biologic + MTX and tofacitinib + MTX compared to MTX, in standard meta-analysis (direct comparisons) or NMA.

Using the NMA, we found no differences when comparing TNF biologic, non-TNF biologic or tofacitinib to each other, or comparing biologics by dose (SD versus HD versus LD).

Serious adverse events (SAEs)

Based on moderate-quality evidence, the results were inconclusive in standard meta-analyses for serious adverse events with biologic + MTX therapy or tofacitinib + MTX compared to MTX/DMARD, with wide confidence intervals encompassing the null effect and evidence of an important increase in serious adverse events. Based on low-quality evidence, results were also inconclusive for TNF biologic + MTX, non-TNF biologic + MTX and tofacitinib + MTX compared to MTX, in standard meta-analysis (direct comparisons) or NMA.

Using the NMA, the rates of serious adverse events were no different when SD biologic was compared with the HD and LD biologic.

Cancer

Based on low-quality evidence from only one study, the results were inconclusive for cancer with biologic + MTX therapy compared to MTX/DMARD in standard meta-analyses, with wide confidence intervals encompassing the null effect and evidence of an important increase in cancer.

Overall completeness and applicability of evidence

We had pre-specified the seven benefits and harms outcomes for this review, and most outcomes except radiographic progression and cancer were reported by several studies included in this systematic review, meta-analysis and NMA. The evidence report is up to date and current, with this 2015 update (date of search, June 2015). Due to the rarity of trials with direct head-to-head comparisons of biologics or tofacitinib in this RA patient population that has experienced unsuccessful treatment with biologics, data from our review provide indirect comparisons of biologics and tofacitinib to each other and to MTX/DMARDs, using the NMA. Results were based primarily on RCTs of less than 12 months' duration.

In comparison to the original 2009 version, the 2015 update has several new key aspects: (1) Instead of six biologics, we included all nine biologics and tofacitinib in this review; (2) we included cancer and serious adverse events as outcomes; (3) we included all doses of biologics and tofacitinib and analyzed by dose; (4) we analyzed outcomes by whether MTX/DMARD was used concomitantly or not; and (5) we used a Bayesian approach rather than a frequentist approach for analyses and reported odds ratios and 95% credible intervals (CrI). Another major difference compared to the 2009 review was that we examined the main results separately by prior MTX/DMARD/biologic-experience in four separate systematic reviews and NMAs (MTX/DMARD-naïve (under review; not yet published), Biologic + MTX/DMARD therapy in MTX/DMARD-experienced (Singh 2016b), Biologic monotherapy in MTX/DMARD-experienced (Singh 2016c) and Biologic-experienced (this review).

Quality of the evidence

The overall quality of the evidence for beneficial outcomes was high or downgraded to moderate due to concerns about imprecision in the direct estimates or indirectness in the NMA estimates. Harms outcomes were downgraded to low mainly for serious concerns about imprecision due to few events except for the direct estimate for serious adverse events which was only downgraded one level to moderate due to imprecision. NMA estimates were downgraded due to concerns of imprecision and indirectness. With only 12 included studies it is difficult to assess publication bias.

Potential biases in the overview process

Our review has several limitations. Lack of reporting of many important outcomes from RCTs (radiographic scores, cancer, etc.) limited our ability to analyze and compare them between biologics. RA remission was frequently assessed using DAS or DAS28 remission, although new definitions, including the ACR-EULAR RA remission definition is now available (Felson 2010), which may be more robust.

To our knowledge there are only few head-to-head comparisons of benefit and safety of various biologics or of biologics and tofacitinib in people with RA. Gabay 2013, Schiff 2008 and Weinblatt 2013a are the most well-known of these, but these head-to-head studies were performed in different patient populations, that is, those who experienced unsuccessful treatment with MTX/DMARD, and not the population of interest for this review, biologic-experienced. We included all direct comparator studies in our analyses that were eligible.

With the introduction of multiple biologics whose benefits have yet to be compared to one another, it is unclear which biologic is more beneficial, safer, and best-tailored to different subgroups of people suffering from RA. In the absence of many direct comparisons, this meta-analysis, and the NMA that provides direct comparisons (standard meta-analyses) as well as indirect comparisons, can provide useful information for patients and health care providers although the results need to be interpreted with caution.

Indirect comparisons that are done in the NMA, have several limitations. RCTs differ in patient population characteristics, most prominently in prior failed therapy, biologic dose, concomitant use of DMARDs, mean RA disease duration, and trial duration. To overcome this limitation, we analyzed in the categories of previous DMARD history (MTX-naive, MTX-experienced, DMARD-experienced and TNF-experienced), biologic dose (SD, HD, LD),

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and concomitant MTX (yes/no). We observed several novel findings when these analyses were performed, which make the results of this NMA and systematic review comprehensive. We also performed pre-specified subgroup analyses by the duration of RA (early, established, late) and duration of the trial (less than six months, six to 12 months, and more than 12 months) as a surrogate of biologic exposure. These analyses also provide interesting results in specific subpopulations of people with RA. However, subgroup analyses are subject to low power and type II error, that is, missing significant results, by chance, due to lower number of studies and participants. Therefore, these results must also be interpreted with caution.

One must be careful in interpreting the odds ratios that may look slightly different from each other numerically, but not statistically. It is important to consider the 95% confidence intervals while interpreting these numbers. Due to a large number of comparisons and challenge interpreting these tables, we summarized all statistically significant odds ratios, to the extent possible, in the main text. This should make it easier for readers to interpret the results.

There is also possibility of type I error, due to multiple comparisons, and up to five differences per 100 comparisons may be due to chance. Being well aware of this study limitation, we determined a priori that the comparisons of interest were groups of drugs (TNF versus non-TNF versus tofacitinib), rather than an individual drug.

However, given the limited data for most outcomes, short trial duration and rarity of harms outcomes, our main concern with most of these analyses is Type-II error, that is, missing an important difference due to small number of events, not Type-I error.

Two abstractors abstracted all data independently for this updated 2015 version and the original 2009 version. This we believe minimizes errors in data abstractions, and biases due to this error. The quality of RCTs was reasonably good, although some RCTs did not report certain quality characteristics and therefore were at higher risk of bias The quality for overall evidence was moderate to high for most outcomes, and low only for withdrawals due to adverse events and cancer. Abstract and titles were also reviewed in duplicate independently, to avoid errors, as part of the systematic review.

Agreements and disagreements with other studies or reviews

Our systematic review, meta-analysis and NMA was performed using a comprehensive strategy, accounting for many potential factors that differ between trials and trial arms, limited to people with RA who had previously experienced biologics. Additionally, our review included nine biologics and tofacitinib in the search, though data were not available for all medications searched (no data for adalimumab or anakinra), while most previous reviews focused on anti-TNF biologics with few exceptions. Most previous systematic reviews or meta-analyses did not stratify participants by prior medication failure and most do not separate the comparators and biologic use by concomitant use of MTX/DMARD. Therefore, direct comparison of results to most published NMAs is not possible.

Several systematic reviews and meta-analyses focused on a different patient population or methodology, or both, and therefore results could not be compared to this review, including:

(1) use of biologics in people previously treated with an inadequate response to conventional DMARDs (Orme 2012); (2) examination of biologic discontinuation rates (Desai 2012); (3) inclusion of only early RA trials with no prior failure of MTX/other DMARDs (Thompson 2011); (4) monotherapy not analyzed separately then biologic + DMARD/MTX (Bongartz 2006; Bongartz 2009; Nixon 2007); and (5) inclusion of all types of studies, including RCTs, observational studies and meta-analyses of traditional DMARDS and biologics for RA (Donahue 2008). Our results agree with several similar analyses in the past, such as no increase in the risk of cancer with biologics compared to DMARDs or placebo (Bongartz 2009; Lopez-Olivo 2012); however, our data are very limited in that only one study provided data on cancer. We recognize that data for harms were few or very few, and therefore our findings are inconclusive. However, our analyses demonstrated the efficacy of biologic monotherapy versus placebo and biologic + MTX versus MTX/DMARD in this RA patient population, who had previously tried a biologic.

AUTHORS' CONCLUSIONS

Implications for practice

Due to limited direct head-to-head comparator trial data for biologics in people with rheumatoid arthritis (RA) whose treatment with a biologic has failed, practitioners are faced with a dilemma in how to choose the next biologic or tofacitinib. This review provides a summary of comparisons of biologics or tofacitinib, as monotherapy to placebo, or in combination with methotrexate (MTX) or disease-modifying anti-rheumatic drugs (DMARDs) to MTX/DMARD, in people with RA whose treatment with a biologic has failed. We found moderate- to high-quality evidence that biologic monotherapy (versus placebo) as well as biologic + MTX (versus MTX/DMARD) were generally efficacious, with inconclusive evidence regarding harms. Specifically, results were inconclusive for withdrawals due to adverse events, serious adverse events and cancer with biologic monotherapy compared to placebo and biologic + MTX therapy compared to MTX/DMARD in standard meta-analyses and NMA, with wide confidence intervals encompassing the null effect and a potentially important increase in each harm. This indicates that more studies are needed for a more confident assessment of relative harms. Overall our review provides support for the use of a second biologic in people previously unsuccessfully treated with a biologic. Only one study provided data on tofacitinib, which limits our confidence in this finding.

Implications for research

We believe that more RCTs of direct head-to-head comparisons of biologics and more studies for tofacitinib, for people with RA who have been unsuccessfully treated with a biologic, are needed. These RCTs should examine the relative benefits and harms of biologics for various stages of the disease (early, established and late RA), various levels of functional limitation (mild, moderate and severe limitation) and the type of prior treatment (TNF versus non-TNF biologic failure) and single versus multiple biologic-failure. More long-term observational studies are needed to study the long-term benefits and harms of biologics.

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ADDITIONAL TABLES
Table 1. Characteristics of included studies

Study name	Biologic(s)	Biologic dose(s)	Number of study arms	Non-biologic comparator	Concomitant use of MTX/DMARD	Trial duration	RA duration	Biologic-naive	Which biologic failed?	Reason(s) for previous biologic-failure	DMARD-naïve	Mono-biologic	Total number of participants
Bingham 2015	Tocilizumab	HD	2	MTX	Yes	5 months	Late	Yes	≥ 1 TNF-biologic	Inefficacy or intolerance	No	Yes	91
Burmester 2013	Tofacitinib	SD, HD	3	MTX + PL	Yes	3 months	Late	No	TNF-biologic	Inadequate response	No	Yes	399
Cohen 2006 (REFLEX)	Rituximab	SD	2	MTX + PL	Yes	24 months	Late	No	≥ 1 TNF-biologic	Inadequate response	No	Yes	520
Emery 2008a (RADIATE)	Tocilizumab	SD, HD	3	MTX + PL	Yes	6 months	Late	No	≥ 1 TNF-biologic	Inefficacy or intolerance	No	Yes	498
Furst 2007	Etanercept/infliximab	SD	2	None	Yes	7 months	Established	No	Etanercept	Partial response	No	No	27
Genovese 2005	Abatacept	SD	2	PL	No	6 months	Late	No	≥ 1 TNF-biologic	Inadequate response	No	Yes	389
Keystone 2008 (RE-FLEX)	Rituximab	SD	2	MTX + PL	Yes	24 months	Late	No	≥ 1 TNF-biologic	Inadequate response	No	Yes	499
Moreland 2002	Abatacept	SD, LD, HD	4	PL	No	3 months	Established	No	Etanercept	Inadequate response	No	Yes	122
Schiff 2014b	Certolizumab	SD	2	PL	No	3 months	Late	No	TNF-biologic except certolizumab	Secondary Inadequate response or intolerance	No	Yes	37
Smolen 2009 (GO-AFTER)	Golilumab	SD, HD	3	DMARD + PL	Yes	6 months	Established	No	TNF-biologic-etanercept, infliximab or adalimumab	Inadequate response (58%) or intolerance (53%)	No	Yes	461

Table 1. Characteristics of included studies *(Continued)*

Weinblatt 2007a	Abata-cept/etan-ercept	SD, LD	2	None	No	12 months	Late	No	Etanercept	Inadequate response	No	No	121
Weinblatt 2008	Etaner-cept	SD, HD	2	None	No	3 months	Late	No	Etanercept 50 mg weekly	Inadequate response	No	Yes	200

DMARD: disease-modifying anti-rheumatic drug
HD: high dose
LD: low dose
MTX: methotrexate
PL: placebo
RA duration: established = mean/median duration 2 to 10 years; late = mean/median duration > 10 years
SD: standard dose

Table 2. Characteristics of excluded studies

Study	Reason for exclusion
Abe 2006	Wrong drug exposure
Axelsen 2015	Duplicate of Hørslev-Petersen 2014
Bae 2013	Wrong drug exposure
Bathon 2000	Duplicate of Genovese 2002
Bejarano 2008	Wrong drug exposure
Bonafede 2015	Not a RCT
Boyle 2015	Wrong exposure
Breedveld 2006	Wrong drug exposure
Bresnihan 1998	Wrong drug exposure
Burmester 2014	Wrong drug exposure
Burmester 2015	Wrong drug exposure
Chen 2009	Wrong drug exposure
Cheng 2014	Conference abstract
Choy 2012	Wrong drug exposure
Cohen 2002	Wrong drug exposure
Cohen 2003	Wrong drug exposure
Cohen 2004	Wrong drug exposure
Combe 2006	Wrong drug exposure
Combe 2009	Wrong drug exposure
Conaghan 2013	Wrong drug exposure
Conaghan 2014	Sub-study of Huizinga 2015
Coombs 2010	Wrong drug exposure
Detert 2013	Wrong drug exposure
Dougados 2013	Wrong drug exposure
Dougados 2014	Duplicate of Huizinga 2015
Doyle 2013	Wrong drug exposure
Durez 2004	Wrong drug exposure

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Table 2. Characteristics of excluded studies *(Continued)*

Durez 2007	Wrong drug exposure
Edwards 2004	Wrong drug exposure
Emery 2006	Wrong drug exposure
Emery 2008a	Wrong drug exposure
Emery 2010	Wrong drug exposure
Emery 2014a	Duplicate
Emery 2014b	Conference abstract
Eriksson 2015	Follow-up at two years of Van Vollenhoven 2012a NCT00764725
Fleischmann 2003	Wrong drug exposure
Fleischmann 2009	Wrong drug exposure
Fleischmann 2012a	Wrong drug exposure
Fleischmann 2012b	Wrong drug exposure
Fleischmann 2013	Conference abstract
Furst 2003	Wrong drug exposure
Furst 2015	Open label study
Gabay 2013	Wrong drug exposure
Gashi 2014	Comparing two doses of a biologic
Genovese 2002	Wrong drug exposure
Genovese 2004	Wrong drug exposure
Genovese 2008	Wrong drug exposure
Genovese 2011	Wrong drug exposure
Genovese 2015	Wrong drug exposure
Gherge 2014	Conference abstract
Goekoop-Ruiterman 2007	Wrong drug exposure
Haraoui 2014	Duplicate of Pope 2014
Heimans 2014	Wrong drug exposure
Hobbs 2015	Wrong drug exposure
Hørslev-Petersen 2014	Open label study

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Table 2.   Characteristics of excluded studies *(Continued)*

Huizinga 2015	Discontinuation study
Iannone 2014	Open label study
Jobanputra 2012	Wrong drug exposure
Johnsen 2006	Wrong drug exposure
Jones 2010	Wrong drug exposure
Kaine 2011	Wrong drug exposure
Kameda 2010	Wrong drug exposure
Kameda 2011	Wrong drug exposure
Kavanaugh 2013	Wrong drug exposure
Kavanaugh 2014	Conference abstract
Kay 2008	Wrong drug exposure
Kennedy 2014	Wrong drug exposure
Keystone 2004a	Wrong drug exposure
Keystone 2004b	Wrong drug exposure
Keystone 2009	Wrong drug exposure
Keystone 2014	Conference abstract
Kim 2007	Wrong drug exposure
Kim 2012	Wrong drug exposure
Kim 2013	Wrong drug exposure
Kivitz 2014	Vaccine response study
Koroleva 2014a	Conference abstract
Koroleva 2014b	Conference abstract
Kremer 2003	Wrong drug exposure
Kremer 2005	Wrong drug exposure
Kremer 2006	Wrong drug exposure
Kremer 2009	Wrong drug exposure
Kremer 2010	Wrong drug exposure
Kremer 2011	Wrong drug exposure

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Table 2. Characteristics of excluded studies *(Continued)*

Kremer 2012	Wrong drug exposure
Kremer 2013	Wrong drug exposure
Kremer 2015	Cross over study design
Lan 2004	Wrong drug exposure
Landewé 2015	Conference abstract
Lipsky 2000	Wrong drug exposure
Lisbona 2008	Wrong drug exposure
Lisbona 2010	Wrong drug exposure
Machado 2014	Wrong drug exposure
Maini 1999	Wrong drug exposure
Maini 2006	Wrong drug exposure
Manders 2015	Trial participants switched therapy within one year/before completion of study period
Mathias 2000	Wrong drug exposure
McInnes 2015	Compared lipid levels in those randomized to CZP or PL, in MTX-IR participants
Miyasaka 2008	Wrong drug exposure
Moreland 1999	Wrong drug exposure
Nam 2014a	Wrong drug exposure
Nam 2014b	Wrong drug exposure
Navarro 2014	Conference abstract
Nishimoto 2004	Wrong drug exposure
Nishimoto 2007	Wrong drug exposure
Nishimoto 2009	Wrong drug exposure
O'Dell 2013	Wrong drug exposure
Oakley 2014	Conference abstract
Pavelka 2013	Sub-group analysis of Smolen 2013 NCT00565409
Pope 2014	Wrong drug exposure
Quinn 2005	Wrong drug exposure
Rantalaiho 2014	Wrong drug exposure

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Table 2. Characteristics of excluded studies *(Continued)*

Rau 2004	Wrong drug exposure
Rigby 2011	Duplicate of Tak 2011
Rubbert-Roth 2010	Wrong drug exposure
Schiff 2008	Wrong drug exposure
Schiff 2013	Wrong drug exposure
Smolen 2008	Wrong drug exposure
Smolen 2013	Wrong drug exposure
Smolen 2014b	Participants in the control group also received the intervention
Smolen 2015	Wrong drug exposure
Sonomoto 2014	Open label study
Soubrier 2009	Wrong drug exposure
St Clair 2004	Wrong drug exposure
Strand 2006	Wrong drug exposure
Strand 2012	Wrong drug exposure
Tada 2012	Wrong drug exposure
Tak 2011	Wrong drug exposure
Tak 2012	Wrong drug exposure
Takeuchi 2013a	Wrong drug exposure
Takeuchi 2013b	Wrong drug exposure
Takeuchi 2013c	Wrong drug exposure
Takeuchi 2014	Wrong drug exposure
Tam 2012	Wrong drug exposure
Tanaka 2011	Wrong drug exposure
Tanaka 2012	Wrong drug exposure
Taylor 2004	Wrong drug exposure
Taylor 2006	Wrong drug exposure
Van de Putte 2003	Wrong drug exposure
Van de Putte 2004	Wrong drug exposure

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Table 2. Characteristics of excluded studies *(Continued)*

Van der Heidje 2006	Wrong drug exposure
Van der Heidje 2007	Wrong drug exposure
Van Der Heijde 2013	Wrong drug exposure
Van der Kooij 2009	Wrong drug exposure
Van Riel 2006	Wrong drug exposure
Van Vollenhoven 2009	Wrong drug exposure
Van Vollenhoven 2012a	Duplicate of Van Vollenhoven 2009
Van Vollenhoven 2012b	Wrong drug exposure
Vital 2015	B cell depletion study
Weinblatt 1999	Wrong drug exposure
Weinblatt 2003	Wrong drug exposure
Weinblatt 2006	Wrong drug exposure
Weinblatt 2012	Wrong drug exposure
Weinblatt 2013a	Wrong drug exposure
Weinblatt 2013b	Wrong drug exposure
Weinblatt 2014	Results at 1 year of Weinblatt 2013b GO-FURTHER trial, NCT00973479
Weisman 2003	Wrong drug exposure
Weisman 2007	Wrong drug exposure
Westhovens 2006	Wrong drug exposure
Westhovens 2009	Wrong drug exposure
Westhovens 2014	Conference abstract
Yamamoto 2014a	Wrong drug exposure
Yamamoto 2014b	Wrong drug exposure
Yamanaka 2014	Post hoc analysis of Takeuchi 2014
Yazici 2012	Wrong drug exposure
Zhang 2006	Wrong drug exposure
Østergaard 2015	Wrong drug exposure

CZP: certolizumab pegol
MTX-IR: methotrexate incomplete responders

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PL: placebo

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Table 3. 'Summary of findings' table for biologics vs. comparator in people previously unsuccessfully treated with biologics (all participants: 1 or more TNF-biologic failed)

Comparison		No. of participants (studies)	Direct evidence	Network meta-analysis			
				Absolute risk difference, NNTB	Quality of evidence		Absolute risk difference, NNTB
Outcome: ACR50			**RR (95% CI)**			**RR (95% CrI)**	
All biologics	vs. placebo	548 (3 studies)	4.10 (1.97 to 8.55)	14% (6% to 21%), NNTB = 8 (4 to 23)	⊕⊕⊕⊝ moderate (downgraded for imprecision)[a]	n/a	
All biologics + MTX	vs. MTX/ DMARD	1479 (3 studies)	4.07 (2.76 to 5.99)	16% (10% to 21%), NNTB = 7 (5 to 11)	⊕⊕⊕⊕ high[b]	n/a	
TNF biologic + MTX	vs. MTX/ DMARD	461 (1 study)	2.84 (1.49 to 5.40)	12% (6% to 18%), NNTB = 9 (5 to 25)	⊕⊕⊕⊝ moderate (downgraded for imprecision)[a]	2.97 (1.38 to 6.41)	10% (2% to 25%), NNTB = 10 (4 to 48)
Non-TNF biologic + MTX	vs. MTX/ DMARD	1018 (2 studies)	4.99 (3.07 to 8.11)	18% (10% to 25%), NNTB = 6 (4 to 10)	⊕⊕⊕⊝ moderate (downgraded for imprecision)[a]	5.07 (3.21 to 8.14)	21% (13% to 30%), NNTB = 5 (3 to 9)
Tofacitinib + MTX	vs. MTX/ DMARD	399 (1 study)	3.24 (1.78 to 5.89)	19% (12% to 26%), NNTB = 6 (3 to 14)	⊕⊕⊕⊝ moderate (downgraded for imprecision)[a]	3.61 (1.74 to 7.24)	13% (4% to 29%), NNTB = 8 (4 to 25)
Outcome: Health Assessment Questionnaire (HAQ) score, 0-3 (higher = worse; A "negative sign" indicates improve-			**MD (95% CI)**				

ment): A measure of function							
All biologics	vs. placebo	n/a					
All biologics + MTX	vs. MTX/DMARD	959 (2 studies)	-0.29 (-0.36 to -0.21)	-9.7% (-12% to -7.0%), NNTB = 5 (4 to 7)	⊕⊕⊕⊕ high[b]	n/a	
TNF biologic + MTX	vs. MTX/DMARD	461 (1 study)	-0.25 (-0.40 to -0.10)	-8.3% (-13% to -3%), NNTB = 5 (7 to 16)	⊕⊕⊕⊕ high[b]	-0.37 (-6.67 to 5.89)	-12.3% (-222.3% to 196.3%), NNTB = n/a
Non-TNF biologic + MTX	vs. MTX/DMARD	498 (1 study)	-0.37 (-0.46 to -0.28)	-12.3% (-15% to -9%), NNTB = 4 (3 to 5)	⊕⊕⊕⊕ high[b]	-0.25 (-6.54 to 5.99)	-8.3% (-218% to 199.7%), NNTB = n/a
Tofacitinib + MTX	vs. MTX/DMARD	399 (1 study)	-0.27 (-0.39 to -0.14)	-9% (-13% to -4.7%), NNTB = 5 (4 to 10)	⊕⊕⊕⊕ high[b]	-0.26 (-6.57 to 5.95)	-8.7% (-219% to 198.3%), NNTB = n/a
Outcome: Remission **(defined as DAS <1.6 or DAS28 <2.6)**			**RR (95% CI)**			**RR (95% CI)**	
All biologics	vs. placebo	389 (1 study)	13.51 (1.85 to 98.45)	9% (5% to 13%), NNTB = 11 (3 to 136)	⊕⊕⊕⊖ moderate (downgraded for imprecision)[a]	n/a	
All biologics + MTX	vs. MTX/DMARD	959 (2 studies)	20.73 (4.13 to 104.16)	10% (8% to 13%), NNTB = 17 (4 to 96)	⊕⊕⊕⊖ moderate (downgraded for imprecision)[a]	n/a	
TNF biologic + MTX	vs. MTX/DMARD	461 (1 study)	16.21 (2.24 to 117.51)	10% (6% to 13%), NNTB = 11 (3 to 110)	⊕⊕⊕⊖ moderate (downgraded for imprecision)[a]	22.27 (3.60 to 400.70)	8% (1% to 52%), NNTB = 9 (2 to 61)

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Table 3. 'Summary of findings' table for biologics vs. comparator in people previously unsuccessfully treated with biologics (all participants: 1 or more TNF-biologic failed)

Non-TNF biologic + MTX	vs. MTX/ DMARD	498 (1 study)	33.72 (2.08 to 546.23)	10% (7% to 14%), NNTB = n/a[e]	⊕⊕⊕⊖ moderate (downgraded for imprecision)[a]	31.20 (6.70 to 456.30)	11% (3% to 32%), NNTB = 18 (3 to 93)
Tofacitinib + MTX	vs. MTX/ DMARD	398 (1 study)	15.44 (0.93 to 256.10)	6% (3% to 9%), NNTB = n/a[e]	⊕⊕⊕⊖ moderate (downgraded for imprecision)[a]	n/a	
Outcome: Radiographic progression	No studies reported this outcome.						
Outcome: Withdrawals due to adverse events			**RR (95% CI)**			**RR (95% CI)**	
All biologics	vs. placebo	428 (2 studies)	0.62 (0.13 to 2.93)	-1% (-4% to 3%), NNTB = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[a,e]	n/a	
All biologics + MTX	vs. MTX/ DMARD	611 (2 studies)	3.32 (0.86 to 12.85)	5% (-3% to 13%), NNTB = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[a,e]	n/a	
TNF biologic + MTX	vs. MTX/ DMARD	n/a					
Non-TNF biologic + MTX	vs. MTX/ DMARD	611 (2 studies)	3.32 (0.86 to 12.85)	5% (-4% to 13%), NNTB = n/a	⊕⊖⊖⊖ very low (downgraded for serious imprecision/inconsistency)[a,d,f]	1.99 (0.80 to 5.98)	3% (-1% to 8%), NNTB = n/a
Tofacitinib + MTX	vs. MTX/ DMARD	399 (1 study)	0.99 (0.41 to 2.39)	0% (-5% to 5%), NNTB = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[a,d]	1.02 (0.29 to 3.65)	0% (-2% to 6%), NNTB = n/a
Outcome: Serious adverse events			**RR (95% CI)**			**RR (95% CI)**	

All biologics	vs. placebo	428 (2 studies)	0.93 (0.51 to 1.68)	-1% (-7% to 5%), NNTB = n/a	⊕⊕⊝⊝ low (downgraded for serious imprecision)[a,d]	n/a	
All biologics + MTX	vs. MTX/ DMARD	1072 (3 studies)	0.69 (0.44 to 1.09)	-2% (-5% to 1%), NNTB = n/a	⊕⊕⊕⊝ moderate (down-graded for imprecision)[a]	n/a	
TNF biologic + MTX	vs. MTX/ DMARD	461 (1 study)	0.55 (0.25 to 1.22)	-3% (-8% to 1%), NNTB = n/a	⊕⊕⊝⊝ low (downgraded for serious imprecision)[a,d]	0.56 (0.20 to 1.51)	-3% (-6% to 3%), NNTB = n/a
Non-TNF biologic + MTX	vs. MTX/ DMARD	611 (2 studies)	0.77 (0.45 to 1.33)	-1% (-6% to 3%), NNTB = n/a	⊕⊕⊝⊝ low (downgraded for serious imprecision)[a,d]	0.85 (0.49 to 1.53)	-1% (-4% to 3%), NNTB = n/a
Tofacitinib + MTX	vs. MTX/ DMARD	399 (1 study)	0.33 (0.09 to 1.15)	-3% (-7% to 1%), NNTB = n/a	⊕⊕⊝⊝ low (downgraded for serious imprecision)[a,d]	0.32 (0.07 to 1.27)	-4% (-8% to 2%), NNTB = n/a
Outcome: Cancer (**note: Peto OR used but can interpret as RR due to low event rate**)			**RR (95% CI)**			**RR (95% CI)**	
All biologics	vs. placebo	n/a					
All biologics + MTX	vs. MTX/ DMARD	550 (2 studies)	4.54 (0.24 to 85.36)	1% (-1% to 2%), NNTB = n/a	⊕⊕⊝⊝ low (downgraded for serious imprecision)[a,d]	n/a	
TNF biologic + MTX	vs. MTX/ DMARD	459 (1 study)	4.54 (0.24 to 85.36)	1% (-1% to 2%), NNTB = n/a	⊕⊕⊝⊝ low (downgraded for serious imprecision)[a,d]		
Non-TNF biologic + MTX	vs. MTX/ DMARD	91 (1 study)	Not es-timable	0% (-5% to 5%), NNTB = n/a	⊕⊕⊝⊝ low (downgraded for serious imprecision)[a,d]		

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Table 3. 'Summary of findings' table for biologics vs. comparator in people previously unsuccessfully treated with biologics (all participants: 1 or more TNF-biologic failed)

Tofacitinib + MTX	vs. MTX/ DMARD	n/a					

Note - no studies reported radiographic progression for either biologic or tofacitinib.

High quality (⊕⊕⊕⊕) : we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality (⊕⊕⊕⊖) : we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality (⊕⊕⊖⊖) : our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality (⊕⊖⊖⊖) : we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; CrI: credible interval; DAS: Disease Activity Score; DMARD: disease-modifying anti-rheumatic drug; MD: mean difference; MTX: methotrexate; n/a: not available; NNTB: number needed to treat for an additional beneficial outcome; RR: risk ration; TNF: tumor necrosis factor

Comparator = placebo and/or MTX and/or DMARD

[a]Downgraded for imprecision - few events (< 300).

[b]No evidence of imprecision or inconsistency. Number of events > 300.

[c]Downgraded for indirectness/intransitivity due to differing participant characteristics (established vs. late RA; types of failures); differing biologic doses and co-interventions; and differing comparators.

[d]Downgraded for imprecision - 95% CI estimate includes both null effect and appreciable benefit or harm.

[e]Could not be calculated, control event % = 0.

[f] I^2 = 73% - downgraded for inconsistency

Table 4. ACR50 analysis for the type of medication (MTX/DMARD active comparator): odds ratios (OR), risk ratios (RR) and risk difference (RD) for all treatment comparisons - random-effects model

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
(MTX or DMARD) + non-TNF	Comparator	6.48 (3.76 to 11.66)	5.07 (3.21 to 8.14)	0.21 (0.13 to 0.30)
(MTX or DMARD) + monoclonal antibodies against TNF		3.32 (1.41 to 8.65)	2.97 (1.38 to 6.41)	0.10 (0.02 to 0.25)
TOFA		4.20 (1.82 to 10.30)	3.61 (1.74 to 7.24)	0.13 (0.04 to 0.29)
(MTX or DMARD) + monoclonal antibodies against TNF	(MTX or DMARD) + non-TNF	0.51 (0.18 to 1.54)	0.59 (0.24 to 1.38)	-0.11 (-0.24 to 0.08)
TOFA		0.65 (0.23 to 1.86)	0.71 (0.31 to 1.58)	-0.07 (-0.22 to 0.12)
TOFA	(MTX or DMARD) + monoclonal antibodies against TNF	1.26 (0.36 to 4.40)	1.21 (0.43 to 3.36)	0.03 (-0.15 to 0.22)
Random-effects model	Residual deviance	8.529 vs. 10 data point		
	Deviance information criteria	65.147		
Fixed-effect model	Residual deviance	8.129 vs. 10 data point		
	Deviance information criteria	64.307		
Note:				
Total participants	2267			
Total studies	5			
2-arm	5			

DMARD: disease-modifying anti-rheumatic drug
MTX: methotrexate
TOFA: tofacitinib
TNF: tumor necrosis factor

Table 5. ACR50 analysis by dose (MTX/DMARD active comparator): odds ratios (OR), risk ratios (RR) and risk difference (RD) for all treatment comparisons - random-effects model

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)

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Table 5. ACR50 analysis by dose (MTX/DMARD active comparator): odds ratios (OR), risk ratios (RR) and risk difference (RD) for all treatment comparisons - random-effects model *(Continued)*

MTX SD biologic	Comparator: MTX or DMARD	4.82 (2.94 to 8.08)	4.10 (2.64 to 6.51)	0.14 (0.09 to 0.20)
MTX HD biologic		7.12 (3.73 to 13.28)	5.55 (3.24 to 9.23)	0.21 (0.12 to 0.31)
MTX HD biologic	MTX SD biologic	1.47 (0.84 to 2.54)	1.35 (0.87 to 2.03)	0.07 (-0.03 to 0.17)
Random-effects model	Residual deviance	10.34 vs. 10 data points		
	Deviance information criteria	64.487		
Fixed-effect model	Residual deviance	11.64 vs. 10 data points		
	Deviance information criteria	64.41		
Total participants	1868			
Total studies	4			
2-arm	2			
3-arm	2			

DMARD: disease-modifying anti-rheumatic drug
HD: high dose
MTX: methotrexate
SD: standard dose

Table 6. ACR50 analysis by dose (placebo comparator): odds ratios (OR), risk ratios (RR) and risk difference (RD) for all treatment comparisons - random-effects model

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
SD	Comparator	3.88 (0.99 to 23.62)	3.41 (0.99 to 14.41)	0.11 (0.00 to 0.39)
HD		4.91 (1.10 to 33.03)	4.14 (1.09 to 17.12)	0.15 (0.01 to 0.47)
HD	SD biologic	1.24 (0.49 to 3.32)	1.19 (0.55 to 2.57)	0.03 (-0.10 to 0.21)
Total partici-pants	359			

Table 6. ACR50 analysis by dose (placebo comparator): odds ratios (OR), risk ratios (RR) and risk difference (RD) for all treatment comparisons - random-effects model *(Continued)*

Total studies	3

HD: high dose
SD: standard dose

Table 7. HAQ analysis (MTX/other DMARD active comparator) for the type of medication: mean difference (MD) for all treatment comparisons - random-effects model

Treatment	Reference	**MD** (95% CrI)
(MTX or DMARD) + non-TNF	Comparator: PL, MTX or DMARD	
(MTX or DMARD) + medications targeting TNF		-0.37 (-6.67 to 5.89)
TOFA		-0.26 (-6.57 to 5.95)
(MTX or DMARD) + medications targeting TNF	(MTX or DMARD) + non-TNF	-0.12 (-8.96 to 8.75)
TOFA		-0.02 (-8.82 to 8.80)
TOFA	(MTX or DMARD) + medications targeting TNF	0.11 (-8.83 to 8.97)
Random-effects model	Residual deviance	5.996 vs. 6 data points
	Deviance information criteria	-13.527
Fixed-effect model	Residual deviance	6.009 vs. 6 data points
	Deviance information criteria	-13.496
Note: A Negative sign indicates improvement in function		
Total participants	1358	
Total studies	3	
2-arm	3	

DMARD: disease-modifying anti-rheumatic drug
MTX: methotrexate
PL: placebo
TOFA: tofacitinib
TNF: tumor necrosis factor

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Table 8. Remission analysis (MTX/DMARD active comparator) for the type of medication: odds ratios (OR), risk ratios (RR) and risk difference (RD) for all treatment comparisons - random-effects model

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
MTX + non-TNF	Comparator	30.61 (6.46 to 346.20)	27.18 (6.13 to 262.70)	0.11 (0.03 to 0.28)
MTX + TNF		23.11 (3.60 to 548.90)	21.04 (3.53 to 287.20)	0.08 (0.01 to 0.52)
MTX + TNF	MTX + non-TNF	0.75 (0.04 to 26.40)	0.77 (0.05 to 13.49)	-0.03 (-0.26 to 0.47)
Random-effects model	Residual deviance	5.167 vs. 6 data points		
	Deviance information criteria	30.949		
Fixed-effect model	Residual deviance	5.271 vs. 6 data points		
	Deviance information criteria	31.163		
Note:				
Total participants	1348			
Total studies	3			
2-arm	2			
3-arm	1			

MTX: methotrexate
TNF: tumor necrosis factor

Table 9. Remission: analysis (MTX/other DMARD active comparator trials) by dose: odds ratio (OR) for all treatment comparisons - random-effects model

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
MTX SD	Comparator	14.92 (3.49 to 96.81)	14.03 (3.40 to 87.45)	0.06 (0.02 to 0.13)
MTX HD		54.62 (11.77 to 402.30)	43.97 (10.54 to 272.50)	0.18 (0.07 to 0.40)
MTX HD	MTX SD	3.62 (1.19 to 12.87)	3.10 (1.16 to 8.95)	0.13 (0.01 to 0.33)

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Table 9. Remission: analysis (MTX/other DMARD active comparator trials) by dose: odds ratio (OR) for all treatment comparisons - random-effects model *(Continued)*

Random-effects model	Residual deviance	8.496 vs. 8 data points
	Deviance information criteria	42.391
Fixed-effect model	Residual deviance	14.72 vs. 8 data points
	Deviance information criteria	46.982
Note:		
Total participants	1348	
Total studies	3	
2-arm	1	
3-arm	2	

HD: high dose
MTX: methotrexate
SD: standard dose

Table 10. Withdrawals due to adverse events: analysis (MTX/other DMARD active comparator trials) for the type of medication: odds ratio (OR) for all treatment comparisons - random-effects model

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
MTX or DMARD + non-TNF	Comparator	2.04 (0.80 to 6.49)	1.99 (0.80 to 5.98)	0.03 (-0.01 to 0.08)
TOFA + MTX		1.02 (0.29 to 3.90)	1.02 (0.29 to 3.65)	0.00 (-0.02 to 0.06)
TOFA + MTX	MTX or DMARD + non-TNF	0.50 (0.09 to 2.55)	0.51 (0.10 to 2.42)	-0.03 (-0.09 to 0.05)
Random-effects model	Residual deviance	9.006 vs. 8 data points		
	Deviance information criteria	42.328		
Fixed-effect model	Residual deviance	9.557 vs. 8 data points		
	Deviance information criteria	42.474		
Note:				

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Table 10.   Withdrawals due to adverse events: analysis (MTX/other DMARD active comparator trials) for the type of medication: odds ratio (OR) for all treatment comparisons - random-effects model *(Continued)*

Total participants	1401
Total studies	4
2-arm	4

DMARD: disease-modifying anti-rheumatic drug
MTX: methotrexate
TOFA: tofacitinib
TNF: tumor necrosis factor

Table 11.   Serious adverse events: analysis (MTX/other DMARD active comparator trials) for the type of medication: odds ratio (OR) for all treatment comparisons - random-effects model

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
(MTX or DMARD) + non-TNF	Comparator	0.84 (0.47 to 1.58)	0.85 (0.49 to 1.53)	-0.01 (-0.04 to 0.03)
(MTX or DMARD) + medications		0.54 (0.19 to 1.56)	0.56 (0.20 to 1.51)	-0.03 (-0.06 to 0.03)
TOFA + MTX		0.31 (0.07 to 1.29)	0.32 (0.07 to 1.27)	-0.04 (-0.08 to 0.02)
(MTX or DMARD) + medications	(MTX or DMARD) + non-TNF	0.64 (0.19 to 2.13)	0.66 (0.20 to 2.02)	-0.02 (-0.07 to 0.05)
TOFA + MTX		0.36 (0.07 to 1.70)	0.38 (0.07 to 1.65)	-0.03 (-0.08 to 0.03)
TOFA + MTX	(MTX or DMARD) + medications	0.56 (0.09 to 3.37)	0.57 (0.09 to 3.21)	-0.01 (-0.08 to 0.05)

Random-effects model	Residual deviance	8.969 vs. 10 data points
	Deviance information criteria	56.677
Fixed-effect model	Residual deviance	8.795 vs. 10 data points
	Deviance information criteria	56.133
Note:		

Total participants	1862
Total studies	5

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Table 11. Serious adverse events: analysis (MTX/other DMARD active comparator trials) for the type of medication: odds ratio (OR) for all treatment comparisons - random-effects model *(Continued)*

2-arm	5

DMARD: disease-modifying anti-rheumatic drug
MTX: methotrexate
TOFA: tofacitinib
TNF: tumor necrosis factor

Table 12. Serious adverse events analysis (MTX/other DMARD active comparator trials) by dose: odds ratio (OR) for all treatment comparisons - random-effects model

Treatment	Reference	**OR** (95% CrI)	**RR** (95% CrI)	**RD** (95% CrI)
MTX SD	Comparator	0.80 (0.48 to 1.36)	0.82 (0.51 to 1.32)	-0.01 (-0.05 to 0.02)
MTX HD		0.48 (0.17 to 1.30)	0.50 (0.18 to 1.27)	-0.04 (-0.08 to 0.02)
MTX HD	MTX SD	0.60 (0.20 to 1.65)	0.62 (0.21 to 1.59)	-0.02 (-0.07 to 0.03)
Random-effects model	Residual deviance	8.024 vs. 9 data points		
	Deviance information criteria	49.853		
Fixed-effect model	Residual deviance	7.837 vs. 9 data points		
	Deviance information criteria	49.137		
Note:				
Total participants	1463			
Total studies	4			
2-arm	3			
3-arm	1			

HD: high dose
MTX: methotrexate
SD: standard dose

APPENDICES

Appendix 1. Standard, approved doses of biologics or tofacitinib for the treatment of RA

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Drug	Standard approved US dose
Abatacept	IV: (10mg/kg every 4 weeks): every 4 weeks intravenously at 500 mg dose in patients < 60 kg, 750 mg in patients 60-100 kg and 1000 mg in patients > 100 kg, after the initial dosing regimen of base-line, 2 and 4-week infusions; SQ: After a single intravenous infusion as a loading dose (as per body weight categories above), 125 mg administered by a subcutaneous injection should be given within a day, followed by 125 mg subcutaneously once a week.
Adalimumab	40 mg subcutaneous every 2 weeks
Anakinra	100 mg subcutaneous every day
Certolizumab	400 mg (given as two subcutaneous injections of 200 mg) initially and at Weeks 2 and 4, followed by 200 mg every other week. For maintenance dosing, CIMZIA 400 mg every 4 weeks can be considered.
Etanercept	25 mg subcutaneous twice weekly
Golimumab	SQ: 50 mg subcutaneous every 4 weeks IV: 2 mg/kg given as an intravenous infusion at weeks 0 and 4, then every 8 weeks
Infliximab	SQ: 3 mg/kg intravenous every 8 weeks after initial dosing at 0, 2 and 6 weeks
Tocilizumab	IV: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg based on clinical response SQ: 162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response for patients < 100 kg and 162 mg administered subcutaneously every week for patients >= 100 kg body weight.
Rituximab	IV: two 1000 mg IV doses 2 weeks apart
Tofacitinib	5 mg twice daily

Abbreviations:

IV: intravenous
SQ: subcutaneous

Appendix 2. List of ongoing clinical trials in the WHO trials register and Clinicaltrials.gov

NCT Number	Title
ACTRN12605000784617	A phase IIIb multi-center, randomized, double-blind study to evaluate remission and joint damage progression in methotrexate naive early erosive RA subjects treated with abatacept plus methotrexate compared with methotrexate
ACTRN12605000785606	A phase II study of abatacept versus placebo to assess the prevention of rheumatoid arthritis (RA) in adult patients with undifferentiated arthritis who are at high risk for the development of RA

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(Continued)

ACTRN12606000248561	A phase 1 randomised double blind, placebo-controlled, single dose, dose escalation study of kb002, a chimeric monoclonal antibody which binds to granulocyte macrophage-colony stimulating factor (gm-csf), in patients with rheumatoid arthritis
ACTRN12608000397314	Multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab versus tocilizumab plus non-biologic disease modifying antirheumatic drugs in patients with active rheumatoid arthritis
ACTRN12609000747224	Extension phase of the multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic disease-modifying anti-rheumatic drugs (DMARDs) who have an inadequate response to current non-biologic DMARD and/or anti tumor necrosis factor (anti-TNF) therapy
ACTRN12610000284066	A longitudinal study of patients with rheumatoid arthritis starting biological therapy; assessment of joint inflammation by use of ultrasonography
ACTRN12611000972921	The hunter Humira and endothelial function in early rheumatoid arthritis trial
ACTRN12611001202954	A comparison of arthroscopic synovial biopsy based targeted biologic therapy versus conventional therapy in rheumatoid arthritis (RA)
ACTRN12614000903684	A randomized, single-blind, single-dose, 3-arm, parallel group study to determine the pharmacokinetic similarity of abp 710 and infliximab (Remicade 'registered trademark') in healthy adult subjects
ACTRN12615000557538	Hunter heart-RA-2 (HHRA-2) study: a randomised controlled trial evaluating the effects of Humira upon cardiovascular risk as measured by endothelial function in patients with rheumatoid arthritis who test positive for anti-CCP antibodies as well as those who test negative for anti-CCP antibodies
ChiCTR-CCC-10001054	Circulating dickkopf-1 (DKK-1) is correlated with bone erosion and inflammation in rheumatoid arthritis
ChiCTR-IIR-16008693	Pharmacokinetics, safety and tolerability study of single dose of abatacept 125mg administered subcutaneously
ChiCTR-INR-16009546	The efficacy and safety of low dose il-2 combined il-6 antagonist therapy in Chinese over-treated patients with rheumatoid arthritis
ChiCTR-TRC-09000383	Efficacy and safety of recombinant human il-1 receptor antagonist in Chinese patients with rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial
ChiCTR-TRC-10001060	Efficacy and safety of infliximab in Chinese patients with rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial
CTRI/2008/091/000295	A clinical trial to study the safety and effectiveness of a monoclonal antibody in combination with methotrexate in patients with active rheumatoid arthritis
CTRI/2012/05/002660	A clinical study to demonstrate safety and efficacy data to support the development of R-TPR-015 (1422015) in patients with active rheumatoid arthritis on stable dose of methotrexate.
CTRI/2013/05/003678	"A randomized controlled study to evaluate pharmacokinetic, pharmacodynamic (efficacy) and safety of rituximab (Zydus) and rituximab (Roche) in patients with rheumatoid arthritis
CTRI/2013/09/003963	Study to compare the safety and efficacy of etanercept of Intas biopharmaceuticals ltd against Enbrel® in patients with active rheumatoid arthritis

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CTRI/2013/10/004040	A study to evaluate efficacy, tolerability and safety of adalimumab (Zydus) and adalimumab (Reference) in patients with rheumatoid arthritis
CTRI/2014/04/004571	A clinical trial to study the effects of two drugs, R-TPR-021 / Humira® in patients with active rheumatoid arthritis on a stable dose of methotrexate
CTRI/2014/07/004742	Phase III clinical trial comparing efficacy and safety of BCD-020 (CJSC BIOCAD, Russia) and Mabthera® (f. Hoffmann-la Roche ltd., Switzerland) in patients with rheumatoid arthritis.
CTRI/2014/09/004954	A clinical trial to study the effects of three anti-cd20 monoclonal antibodies in patients with moderate to severe active, seropositive rheumatoid arthritis with an inadequate response to methotrexate based therapy.
CTRI/2015/01/005398	A study to determine pharmacodynamics (effect of drug in the body) and to compare pharmacokinetics (how drug behaves in the body), Safety and tolerability of single dose of Lupin's Rituximab with Roche's Rituximab following I.V. infusion in Patients with Rheumatoid Arthritis
CTRI/2016/02/006625	A clinical trial to evaluate efficacy and safety of BMO-2 and adalimumab in patient with active rheumatoid arthritis
CTRI/2016/04/006884	A clinical study to evaluate the efficacy, safety, immunogenicity, and pharmacokinetics of subcutaneous injection of adalimumab (test product, Hetero) and reference medicinal product (reference product, Abbvie) concomitantly administered with methotrexate in patients with rheumatoid arthritis
CTRI/2016/05/006899	A study to compare the biosimilar of Etanercept (coded as YLB113) made by YLBiologics with Enbrel (originator's Etanercept) in patients suffering from rheumatoid arthritis with respect to its efficacy, safety and antibody formation.
CTRI/2016/07/007097	Multi-centre, randomized, double-blind, two-arm, parallel group, comparative clinical study to evaluate pharmacokinetic, efficacy and safety of etanercept in patients with active rheumatoid arthritis
DRKS00011083	Clinical study of an anthroposophic treatment strategy for early rheumatoid arthritis, compared to conventional long-term therapy
EUCTR2004-000563-96-HU	A 24-month, randomized, double-blind, two period study to evaluate the efficacy and safety of the combination of etanercept and methotrexate and methotrexate alone in subjects with active early rheumatoid arthritis: combination of methotrexate and etanercept
EUCTR2004-000922-59-SE	A phase III, multi-center, randomized, double-blind, placebo-controlled comparative study of abatacept or infliximab in combination with methotrexate in controlling disease activity in subjects with rheumatoid arthritis having an inadequate clinical response to methotrexate.
EUCTR2004-002620-18-DE	A multi-national randomized, double-blind, exploratory study of abatacept versus placebo in preventing the development of rheumatoid arthritis in adult subjects with undifferentiated inflammatory arthritis at high risk for the development of rheumatoid arthritis
EUCTR2004-002993-49-HU	A phase III multicentre, double blind, placebo-controlled, parallel group 52-week study to assess the efficacy and safety of 2 dose regimens of lyophilised cdp870 given subcutaneously as additional medication to methotrexate in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate.
EUCTR2004-003295-10-GB	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously, in methotrexate-naïve subjects with active rheumatoid arthritis - na

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EUCTR2004-003296-36-DE	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously, in subjects with active rheumatoid arthritis despite methotrexate therapy - na
EUCTR2004-003299-12-FI	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously, in subjects with active ankylosing spondylitis - na
EUCTR2004-003733-14-FI	A study investigating whether tocilizumab (study drug) prevents joint damage, and how safe it is, in patients with moderate to severe rheumatoid arthritis randomly divided to groups receiving treatment with tocilizumab and methotrexate or methotrexate and placebo.
EUCTR2004-003741-40-AT	A randomized, double-blind, parallel group study of the safety and reduction of signs and symptoms during treatment with mra versus placebo, in combination with methotrexate, in patients with moderate to severe active rheumatoid arthritis.
EUCTR2004-003771-37-HU	A double-blind, randomized, placebo controlled, dose escalation, multi-center phase I/II trial of humax-cd20, a fully human monoclonal anti-cd20 antibody, in patients with active rheumatoid arthritis who have previously failed one or more disease modifying anti-rheumatic drugs. - humax-cd20 in active rheumatoid arthritis, phase I/II
EUCTR2004-005210-37-DE	A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA versus placebo, in combination with traditional DMARD therapy in patients with moderate to severe active rheumatoid arthritis and an inadequate response to current DMARD therapy.
EUCTR2005-000492-18-IT	Insulin resistance and endothelial dysfunction TNF-alpha dependent in patients with rheumatoid arthritis or metabolic syndrome
EUCTR2005-000674-43-GB	An open label study of the effect of treatment with rituximab on resistant rheumatoid arthritis: clinical, radiological, synovial and immunological outcomes - rituximab in rheumatoid arthritis
EUCTR2005-000784-26-GB	A phase IIIb multi-center, randomized, double-blind study to evaluate remission and joint damage progression in methotrexate naive early erosive RA subjects treated with abatacept plus methotrexate compared with methotrexate revised protocol 04
EUCTR2005-000884-25-DE	A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA versus placebo, in combination with methotrexate in patients with moderate to severe active rheumatoid arthritis and an inadequate response to previous anti-TNF therapy.
EUCTR2005-001138-33-LT	A randomized, double-blind, double-dummy, parallel group study of the safety and efficacy of mra monotherapy, versus methotrexate (MTX) monotherapy, in patients with active rheumatoid arthritis.
EUCTR2005-001549-41-HU	A randomised, double-blind study comparing the safety and efficacy of etanercept with sulphasalazine in subjects with ankylosing spondylitis - ASCEND
EUCTR2005-001633-14-DK	Randomised, multi-center, open-label, parallel-group study comparing adalimumab (Humira?) 40 mg s.c. Eow versus infliximab (Remicade®) 3 mg/kg i.v. Every 6. Week in RA patients with unsustainable clinical response to infliximab 3 mg/kg every 8. Week - The SWITCH Study
EUCTR2005-001742-16-GB	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously in subjects with active rheumatoid arthritis and previously treated with biologic anti-TNFalfa agent(s) - go-after
EUCTR2005-001889-13-SE	Randomised controlled trial evaluating strategies to optimize disease activity control in RA patients treated with infliximab in clinical practice. - RE3

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EUCTR2005-002326-63-LT	A phase III multi–center, double–blind, placebo–controlled, parallel group 24–week study to assess the efficacy and safety of two dose regimens of liquid certolizumab pegol as additional medication to methotrexate
EUCTR2005-002392-32-IE	A randomised, placebo controlled, double-blind, parallel group, international study to evaluate the safety and efficacy of rituximab (Mabthera/Rituxan) in combination with methotrexate, compared to methotrexate monotherapy, in patients with active rheumatoid arthritis.
EUCTR2005-002395-15-FI	A randomized, phase 3, controlled, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of rituximab in combination with methotrexate (MTX) compared to MTX alone, in methotrexate-naïve patients with active rheumatoid arthritis.
EUCTR2005-002396-33-ES	A randomised, double-blind, international study to evaluate the efficacy and safety of various re-treatment regimens of rituximab in combination with methotrexate in RA patients with an inadequate response to methotrexate.
EUCTR2005-002423-13-DE	Long-term extension study of safety during treatment with tocilizumab (MRA) in patients completing treatment in WA17822
EUCTR2005-002909-23-ES	Long-term extension study of safety during treatment with tocilizumab (MRA) in patients completing treatment in MRA core studies.
EUCTR2005-003632-22-ES	A study of the pharmacokinetic and pharmacodynamic activity of rituximab in combination with methotrexate (MTX) in synovial tissue and in peripheral blood of patients with rheumatoid arthritis.
EUCTR2005-004530-40-AT	Induction of remission in RA patients at low disease activity by additional infliximab-therapy
EUCTR2005-004582-41-GB	Safety and efficacy of combination treatment with rituximab and leflunomide in patients with active rheumatoid arthritis - rituximab and leflunomide in RA
EUCTR2005-005013-37-GB	A multi-centre randomised double dummy double blind study comparing two regimens of combination induction therapy in early DMARD naive rheumatoid arthritis: the IDEA study (infliximab as induction therapy in early rheumatoid arthritis) - IDEA
EUCTR2005-005358-27-GB	Efficacy of rituximab (Mabthera) in active ankylosing spondylitis: a clinical and magnetic resonance imaging study - rituximab in as
EUCTR2006-000363-28-GB	Differentiating the mechanism of action of anti TNF-alpha agents - data study
EUCTR2006-000854-32-AT	Rituximab in rheumatoid arthritis in patients who failed therapy with TNF-blockers
EUCTR2006-001000-37-DE	Efficacy and safety of rituximab in patients with rheumatoid arthritis - FIRST
EUCTR2006-001428-38-GB	Remission induction in very early rheumatoid arthritis (RIVERA): a comparison of etanercept plus methotrexate plus steroid with standard therapy - RIVERA
EUCTR2006-001553-10-BE	A 26-week, phase II, multi-center, randomized, double-blind, placebo-controlled study to assess the response to treatment (acr50) and to determine a biomarker profile in responders to ACZ885 (anti-interleukin-1beta monoclonal antibody) plus MTX as compared to MTX alone in early rheumatoid arthritis patients - 2204
EUCTR2006-003843-22-IT	Prospective study on intensive early rheumatoid arthritis treatment with adalimumab: induction of remission and maintenance - 'CURE' A phase IV multicenter, randomized, double-blind study
EUCTR2006-004139-31-BE	A multicenter, randomized, double-period, double-blind study to determine the optimal protocol for treatment initiation with methotrexate and adalimumab combination therapy in patients with early rheumatoid arthritis - OPTIMA

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EUCTR2006-004673-98-HU	Efficacy of rituximab treatment in patients with rheumatoid arthritis having inadequate response to TNF blocker
EUCTR2006-005137-38-FR	A 3 month, randomised, open label, parallel group, descriptive study to explore and compare perceptions and satisfaction for two different delivery mechanisms for etanercept (etanercept autoinjector and the etanercept prefilled syringe)
EUCTR2006-005157-29-FR	Effet du methotrexate sur la relation dose - effet de l'infliximab dans la spondylarthrite ankylosante - SPAXIM
EUCTR2006-005386-19-BE	Cytokines and inflammatory proteins gene expression study in synovial biopsies from rheumatoid arthritis patients refractory to anti-TNF therapy treated with rituximab - anti TNF resistant RA / RTX / mini
EUCTR2006-005640-81-GB	A placebo controlled study of the effect of extended treatment with rituximab on resistant rheumatoid arthritis: - EXXTRA
EUCTR2006-006127-40-GB	Cerebral blood flow following TNF-alpha antagonism in rheumatoid arthritis - a pilot study - TNF/cbf in RA
EUCTR2006-006186-16-NL	Improved: Induction therapy with methotrexate and prednisone in rheumatoid or very early arthritic disease a randomized clinical trial in patients with recent-onset arthritis to compare the efficacy of DMARD combination therapy including prednisone with combination therapy including adalimumab, a TNF-blocking agent - IMPROVED
EUCTR2006-006275-21-GB	A randomised, pragmatic, open-label study of adalimumab versus etanercept for rheumatoid arthritis. - adalimumab versus etanercept for RA
EUCTR2006-006591-37-BE	A 3 month, randomised, open label, parallel group, descriptive study to explore and compare perceptions and satisfaction for two different delivery mechanisms for etanercept (etanercept auto-injector and the etanercept prefilled syringe)
EUCTR2006-006746-33-DE	Re-treatment with rituximab in patients with rheumatoid arthritis who have had an inadequate response to not more than one a TNF (extension study to ML19070) - efficacy of re-therapy in anti-TNFalpha IR
EUCTR2007-000082-38-DK	The OPERA Study. Optimized treatment algorithm in early rheumatoid arthritis: Methotrexate and intra-articular glucocorticosteroid plus adalimumab or placebo in the treatment of early rheumatoid arthritis. A Randomised, double-blind and placebo-controlled, two arms, parallel group study of the additive effect of adalimumab concerning inflammatory control and inhibition of erosive development. - The OPERA Study
EUCTR2007-000593-24-GB	An open-label, observational study of the effects of anti-TNF therapy on peripheral blood and synovial biomarkers in patients with active rheumatoid arthritis.
EUCTR2007-000828-40-FR	A phase IIIb, multi-centre, double-blind randomized, placebo-controlled, parallel group 52-week study to evaluate safety and efficacy of the PEGylated anti-TNFα Fab'fragment, certolizumab pegol, administered concomitantly with stable-dose DMARDs in patients with moderate to low disease activity rheumatoid arthritis.
EUCTR2007-000896-41-HU	A randomized, double-blind study comparing the safety and efficacy of once-weekly administration of etanercept 50 mg, etanercept 25 mg, and placebo in combination with methotrexate in subjects with moderately active rheumatoid arthritis
EUCTR2007-001190-28-GB	Randomised controlled trial of tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis - TACIT

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EUCTR2007-001420-12-BE	A randomised, double-blind (with open comparator etanercept limb), placebo-controlled, phase IIb, multicentre study to evaluate the efficacy of 4 doses of azd9056 administered for 6 months on the signs and symptoms of rheumatoid arthritis
EUCTR2007-001585-33-LT	A randomized, placebo controlled, multicenter clinical study investigating efficacy of rituximab (Mabthera®/Rituxan®) in the inhibition of joint structural damage assessed by magnetic resonance imaging in patients with rheumatoid arthritis and inadequate response to methotrexate - the R.A. Score study. - R.A. Score
EUCTR2007-001625-10-HU	An open-label, randomized study to evaluate the radiographic efficacy and safety of Enbrel™ (etanercept) added to methotrexate in comparison with usual treatment in subjects with moderate rheumatoid arthritis disease activity. - EXTRA
EUCTR2007-001754-11-IT	Pilot study to evaluate the effect of rituximab in combination with MTX in the inhibition of progression of synovitis, bone marrow edema, and erosions evaluated by magnetic resonance imaging (MRI) in the hand of patients with rheumatoid arthritis. - nd
EUCTR2007-002066-35-HU	A phase 2B, randomized, double-blind, placebo controlled active comparator, multicenter study to compare 5 dose regimens of CP-690,550 and adalimumab versus placebo, administered for 6 months in the treatment of subjects with active rheumatoid arthritis
EUCTR2007-002536-29-FR	A randomised, double-blind, placebo controlled, multi-centre phase II study of atacicept in anti-TNF alfa-naïve patients with moderate to severely active rheumatoid arthritis and an inadequate response to methotrexate - atacicept in anti-TNF alfa-naïve subjects with RA
EUCTR2007-003096-39-IT	Effects of etanercept on endothelial function and carotid intima-media thickness in patients with active ankylosing spondylitis: a 52-weeks, randomized, double blind, placebo-controlled study - crest
EUCTR2007-003288-36-NL	A phase 4, multicenter, open-label, assessor-blinded, switch study of the efficacy and safety of infliximab (Remicade) in patients with active rheumatoid arthritis who are responding inadequately to etanercept (Enbrel) of adalimumab (Humira) - restart
EUCTR2007-003358-27-DE	Phase III, multi-center, randomized, double blind, placebo-controlled study for treatment of juvenile ankylosing spondylitis with adalimumab - Humira Study
EUCTR2007-003623-20-ES	Estudio de los efectos de la terapia anti-célula b (rituximab) sobre la inmunopatología del tejido sinovial y las células b de sangre periférica en artritis reumatoide (estudio tesice-ar). Study of the b-cell-targeted therapy (rituximab) effects on the synovial tissue inmunopathology and peripheral blood b cells in rheumatoid arthritis (tesice-ar study).
EUCTR2007-003647-75-NL	A randomised, double-blind, placebo controlled, multi-centre, exploratory, pilot, phase II trial of 150 mg atacicept given subcutaneously in combination with rituximab in subjects with rheumatoid arthritis. - atacicept in combination with rituximab in subjects with rheumatoid arthritis
EUCTR2007-004694-26-BE	A comparative study of a 6-month infliximab (Remicade) or placebo regimen in undifferentiated arthritis at high risk for the development of rheumatoid arthritis : clinical, radiological (MRI) and synovial benefit p1200/001. - infliximab (Remicade) in ua
EUCTR2007-005464-26-GB	Development of heart and blood vessel problems in patients with conditions which cause long-term, widespread, inflammation in the body.
EUCTR2007-005905-23-DE	A multi-center, randomized, double-blind, placebo-controlled study comparing 80 mg of adalimumab with placebo, and demonstrating the non-inferiority of monthly 80 mg adalimumab dosing compared with 40 mg adalimumab every other week dosing
EUCTR2007-006657-63-FI	Study comparing the effect on disease activity when reducing or discontinuing etanercept in subjects with rheumatoid arthritis (RA) (dosera)

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EUCTR2007-007539-14-CZ	A randomised, double-blind, placebo-controlled, phase IIb dose-ranging study (with open-label etanercept treatment group) to investigate efficacy, safety and pharmacokinetics of azd5672 administered for 12 weeks to rheumatoid arthritis patients receiving
EUCTR2008-000105-11-DE	Effectiveness after 4 and 24 weeks and safety of tocilizumab in patients with active RA - TAMARA - tocilizumab and DMARDs: achievements in rheumatoid arthritis
EUCTR2008-000587-17-GB	Multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARD and/or anti-TNF therapy
EUCTR2008-001241-26-HU	A randomized, placebo-controlled, double-blind, dose escalation study to evaluate the efficacy, safety and tolerability of the study drug bt971 in patients with rheumatoid arthritis receiving concomitant methotrexate - n.a.
EUCTR2008-002381-55-ES	Evaluación de la eficacia de rituximab en pacientes con artritis reumatoide a través de la medición, por resonancia magnética de mano, de los parámetros clínicos de la enfermedad. Estudio resonar. Efficacy of rituximab in patients with rheumatoid arthritis, by measurement of disease parameters through magnetic resonance of the hand. RESONAR study.
EUCTR2008-002623-85-NL	A 3-phase study to evaluate sustained remission and productivity outcomes in subjects with early rheumatoid arthritis initiated on treatment with etanercept plus methotrexate
EUCTR2008-002631-33-GB	Randomized, placebo controlled, double blind, multi-center phase II proof-of-concept study to assess the efficacy of ain457 in patients with moderate to severe ankylosing spondylitis - cain457a2209
EUCTR2008-003011-12-GB	Prospective randomised double-blind placebo controlled study assessing the efficacy of tocilizumab with synovial analysis in patients with rheumatoid arthritis - TOCRA
EUCTR2008-004126-16-FI	Local open-label study to evaluate the safety and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARDs
EUCTR2008-004931-39-PL	A study to determine the safety, efficacy, and pharmacokinetics of 80 mg, 160 mg, and 320 mg ald518 versus placebo administered as multiple intravenous infusions to patients with active rheumatoid arthritis who have had an inadequate response to methotrexate.
EUCTR2008-005212-40-SE	Pain mechanisms and fatigue in rheumatoid arthritis (RA) and healthy volunteers. Can antirheumatic and biological therapy affect pain processing and fatigue in RA? - RA pain processing
EUCTR2008-005320-81-AT	A 2-year open-label second extension study to evaluate the safety, tolerability and efficacy of canakinumab (acz885) an anti-interleukin-1ß monoclonal antibody in patients with active rheumatoid arthritis - a2201e2
EUCTR2008-005450-20-BE	The cost-effectiveness of abatacept, rituximab or anti-TNF alpha for patients with rheumatoid arthritis. - Dutch Rheumatoid Arthritis Monitoring (DREAM) Targeted Immune Modulator Evaluation (TIME)
EUCTR2008-005525-11-ES	Estudio randomizado, controlado con placebo, doble ciego y con grupos paralelos para comparar la seguridad y la reducción de la actividad de la enfermedad con la combinación de rituximab (Mabthera) y tocilizumab (roactemra) frente al tratamiento con tocilizumab en pacientes con artritis reumatoide activa con respuesta incompleta a metotrexato. A randomized, placebo controlled, double-blind, parallel group study to compare the safety and efficacy of the combination of rituximab (Mabthera) and tocilizumab (Actemra) versus tocilizumab therapy in patients with active rheumatoid arthritis with an incomplete response to methotrexate.

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EUCTR2008-006256-22-FR	Evaluation by high resolution micro computerized tomography of bone microarchitecture changes in patients with rheumatoid arthritis under anti-TNF therapy.
EUCTR2008-006885-27-NL	Efficacy and safety of adalimumab (Humira®) in patients with peripheral spondyloarthritis without ankylosing spondylitis or psoriatic arthritis
EUCTR2008-006924-68-AT	Extension phase of the multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARD and/or anti-TNF therapy. - this is an extension study to MA21573
EUCTR2008-006936-37-HU	A randomized, parallel, double-blind, placebo-controlled study to evaluate the efficacy and safety of ILV-094 administered subcutaneously to subjects with active rheumatoid arthritis on a stable background of methotrexate
EUCTR2008-008338-35-CZ	Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP 690,550 in patients with active rheumatoid arthritis on background methotrexate
EUCTR2009-010582-23-DE	A golimumab phase 3b, multicenter, switch assessment of subcutaneous and intravenous efficacy in rheumatoid arthritis patients who have inadequate disease control despite treatment with etanercept (Enbrel®) or adalimumab (Humira®)
EUCTR2009-010955-29-NL	Prevention of clinically manifest rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease.
EUCTR2009-011105-17-IT	A single-arm, open-label study of early improvement of anemia and fatigue during treatment with tocilizumab (TCZ) in combination with non biologic DMARDs, in adult patients with moderate to severe active rheumatoid arthritis. - anemia fatigue
EUCTR2009-011137-26-DE	An open-label study assessing the addition of subcutaneous golimumab (GLM) to conventional disease-modifying antirheumatic drug (DMARD) therapy in biologic-naïve subjects with rheumatoid arthritis (part 1), followed by a randomized study assessing the val
EUCTR2009-011520-53-SK	Evaluation of adherence and persistence to tocilizumab in combination with methotrexate or tocilizumab monotherapy in patients with moderate to severe active rheumatoid arthritis in local environment
EUCTR2009-011591-30-GB	An open-label non-randomized extension study to evaluate the safety and tolerability of ain457 (anti interleukin-17 monoclonal antibody) in patients with moderate to severe ankylosing spondylitis - a2209e1
EUCTR2009-011719-19-FR	Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis (axial spa)
EUCTR2009-012185-32-IT	Open label, multicentric phase IIIb study to evaluate the effect of tocilizumab in combination with DMARDs in the inhibition of progression of synovitis, bone marrow edema, and erosions evaluated by dedicated magnetic resonance imaging (MRI) in the hand of patients with rheumatoid arthritis (RA) - ND
EUCTR2009-012204-42-IE	A randomized, double-blind, placebo-controlled, parallel group study to investigate the ability of gsk706769 to maintain clinical efficacy after withdrawal of Enbrel in patients with rheumatoid arthritis
EUCTR2009-012218-30-PT	A randomized, double-blind, placebo-controlled study to assess the efficacy of tocilizumab (TCZ) + non-biological DMARD in reducing synovitis as measured by magnetic resonance imaging (MRI) at 12 weeks after initiation of treatment in patients with moderate to severe rheumatoid arthritis (RA) with inadequate response to non-biological DMARDs - portrait

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EUCTR2009-012759-12-GB	A multi-center, randomized, double-blind, parallel group study of the safety, disease remission and prevention of structural joint damage during treatment with tocilizumab (TCZ), as a monotherapy and in combination with methotrexate (MTX), versus methotrexate in patients with early, moderate to severe rheumatoid arthritis.
EUCTR2009-013316-12-NL	A multi-center, randomized, double blind, placebo controlled study to evaluate remission in DMARD and biological naïve early rheumatoid arthritis (RA) subjects treated with tocilizumab (TCZ) plus tight control methotrexate (MTX) treatment, TCZ monotherapy or tight control MTX monotherapy. - U-ACT-EARLY
EUCTR2009-013758-33-SE	Multicenter study with a 16-week double-blind, placebo-controlled (during the initial 2 weeks) randomized period, followed by a 24-week open label extension to assess magnetic resonance image-verified early response to certolizumab pegol in subjects with
EUCTR2009-015515-40-NL	Prevention of the progression of very early symptoms into ankylosing spondylitis: a placebo controlled trial with etanercept - prevas
EUCTR2009-015653-20-NL	Prospective study on the effects of etanercept treatment in patients with rheumatoid arthritis who are naïve for TNF-alpha blocking therapy and patients who do not respond (anymore) to prior treatment with other anti-TNF-alpha medication - not applicable
EUCTR2009-015740-42-DE	A phase 3, multicenter, randomized, open, prospective, controlled, parallel-group study of reduction of therapy in patients with rheumatoid arthritis in ongoing remission RETRO – reduction of therapy in RA patients in ongoing remission, reduzierung der therapie bei RA-patienten in remission - RETRO
EUCTR2009-015845-21-GB	A multi-center, randomized, blinded, parallel-group study of the reduction of signs and symptoms during monotherapy treatment with tocilizumab 8 mg/kg intravenously versus adalimumab 40 mg subcutaneously in patients with rheumatoid arthritis
EUCTR2009-015950-39-DE	Rituximab-treatment in addition to leflunomide in patients with active rheumatoid arthritis
EUCTR2009-016789-10-NL	Efficacy of the H1N1 flu (swine flu) vaccination in patients with rheumatoid arthritis treated with rituximab
EUCTR2009-017325-19-FI	The effect of six months adalimumab treatment on sick leaves and retirement in patients with rheumatoid arthritis who are at risk of losing their ability to work
EUCTR2009-017443-34-GB	A ph II/III seamless, multi-center, randomized, double-blind, placebo-controlled study of the reduction in signs and symptoms and inhibition of structural damage during treatment with tocilizumab versus placebo in patients with ankylosing spondylitis who have failed non-steroidal anti-inflammatory drugs and are naïve to TNF antagonist therapy
EUCTR2009-017488-40-GB	A randomized, double-blind, parallel-group placebo-controlled study of the safety and reduction of signs and symptoms during treatment with tocilizumab (TCZ) versus placebo in patients with ankylosing spondylitis who have had an inadequate response to previous TNF antagonist therapy
EUCTR2010-018331-18-GB	A 52 week, single center, open-label study to evaluate neutrophil function and survival effects of tocilizumab (TCZ) in patients with active rheumatoid arthritis (RA) on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARD and/or anti-TNF therapy
EUCTR2010-018375-22-ES	A randomized, double-blind, parallel group study of the safety and effect on clinical outcome of tocilizumab sc versus tocilizumab iv, in combination with traditional disease modifying anti-rheumatoid arthritis drugs (DMARDs), in patients with moderate to severe active rheumatoid arthritis. Estudio randomizado, doble ciego, con grupos de tratamiento paralelos, para evaluar la seguridad y el efecto sobre el resultado clínico de tocilizumab sc frente a tocilizumab iv en combi-

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	nación con fármacos antirreumáticos modificadores de la enfermedad (FAMEs) tradicionales, en pacientes con artritis reumatoide activa moderada a severa.
EUCTR2010-018646-31-LV	Recruitment status
EUCTR2010-019694-15-BE	Act-alone : an open-label, single-arm study to describe glucocorticoid use in rheumatoid arthritis patients treated with tocilizumab in daily clinical practice and to evaluate systematic glucocorticoid dose reduction once low disease activity is reached - act-alone
EUCTR2010-019873-13-BE	Comparative study of the clinical response and cardiorespiratory endurance in early rheumatoid arthritis patients treated with tociluzimab or methotrexate addendum protocol : global gene expression profiles in synovial biopsies from early rheumatoid arthritis patients treated with tocilizumab or methotrexate -TOMERA
EUCTR2010-019935-37-FI	A pragmatic, randomized, parallel group study of the effect on disease remission, work productivity, and tolerability of tocilizumab in combination with DMARDs and individually designed best practice DMARD therapy in patients with early, moderate to severe rheumatoid arthritis
EUCTR2010-020738-24-GB	To see whether for patients with established rheumatoid arthritis that have already achieved a good response to tumour necrosis factor inhibitor (TNF inhibitor) treatment, whether the treatment be tapered to a minimum dose without affecting the control of disease activity
EUCTR2010-020839-39-GB	Efficacy and safety of cdp6038 in patients with rheumatoid arthritis with an unsuccessful response to anti-TNF therapy
EUCTR2010-020913-10-GB	An open label, pilot, multi-centre, step-down, randomised controlled trial to examine whether etanercept 25mg once weekly is effective in maintaining a clinical response in patients with ankylosing spondylitis who have responded to 50mg once weekly - answ
EUCTR2010-021020-94-DE	A randomized, double-blind, parallel-group, placebo- and active calibrator-controlled study assessing the clinical benefit of sar153191 subcutaneous (sc) on top of methotrexate (MTX) in patients with active rheumatoid arthritis (RA) who have failed previo text missing here - title incomplete
EUCTR2010-022049-88-DE	"Efficacy and safety study of a sequential therapy of tocilizumab (TCZ) and, if initially inadequately responded to tocilizumab (TCZ), followed by rituximab (RTX) in DMARD-ir patients with rheumatoid arthritis (MIRAI)" - MIRAI
EUCTR2010-022378-15-DE	A clinical study to explore the therapeutic effects of different doses of the new drug veltuzumab, a drug of biologic origin, and placebo, in patients with rheumatoid arthritis.
EUCTR2010-023910-30-GB	A prospective, single-centre, randomised study evaluating the clinical, imaging and immunological depth of remission achieved by very early versus delayed etanercept in patients with rheumatoid arthritis (VEDERA) - very early versus delayed etanercept in
EUCTR2010-023956-99-HU	Phase IIB rheumatoid arthritis dose ranging study for BMS-945429 in subjects who are not responding to methotrexate
EUCTR2011-000215-79-FR	Tociluzimab effect on endothelial function in patients with rheumatoid arthritis - TEFRA
EUCTR2011-001626-15-ES	A study of Roactemra/Actemra (tocilizumab) in combination with methotrexate in patients with rheumatoid arthritis with inadequate response to prior treatment with methotrexate and low disease activity with the combination de Roactemra/Actemra y methotrexate.
EUCTR2011-001729-25-DE	Study designed to demonstrate the efficacy and safety of certolizumab pegol in combination with methotrexate in the treatment of subjects suffering from early, progressive active rheumatoid arthritis.

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EUCTR2011-001863-39-AT	A study of safety and efficacy of tocilizumab (TCZ) in combination with methotrexate (MTX) versus tocilizumab monotherapy in patients with mild to moderate rheumatoid arthritis, who have not adequately responded to their current treatment with MTX.
EUCTR2011-002275-41-CZ	A study of two different adalimumab formulations in adults with rheumatoid arthritis
EUCTR2011-002325-22-GB	Study of ixekizumab in participants with active ankylosing spondylitis (AS)
EUCTR2011-002363-15-IS	A clinical trial with the aim to explore infusion reactions from tocilizumab given either in 31 or 60 minutes to patients with moderate to severe rheumatoid arthritis.
EUCTR2011-004017-17-GB	Tocilizumab and remission in early rheumatoid arthritis
EUCTR2011-004171-36-CZ	A study comparing sait101 to Mabthera® in subjects with severe rheumatoid arthritis (RA)
EUCTR2011-004468-31-GB	Evaluating the long-term safety and efficacy effects of ct-p13 together with methotrexate in patients with arthritis
EUCTR2011-005021-48-HU	A study to investigate and compare the efficacy, safety, tolerability and pharmacodynamic (biochemical and physiological effects of the drug) of tl011 and Mabthera® (rituximab) in patients with severe, active rheumatoid arthritis treated with methotrexate (MTX)
EUCTR2011-005204-15-AT	Could ultrasound help to identify the patients with rheumatoid arthritis, in those the treatment with biological DMARDs could be stopped?
EUCTR2011-005260-20-GB	Roactemra® (tocilizumab) plus methotrexate (MTX) in stable dosage in comparison with Roactemra® plus reducing (tapering) MTX dosages in patients with severe rheumatoid arthritis (RA) that have inadequate responded to a trial of two disease modifying anti-rheumatic drugs (DMARDs), including MTX and have not been previously treated with a biologic agent, such as a TNF inhibitor.
EUCTR2011-005448-87-HU	A study of the maintenance of efficacy of etanercept plus DMARD(s) compared with DMARD(s) alone in subjects with rheumatoid arthritis after achieving an adequate response with etanercept plus DMARD(s)
EUCTR2011-005649-10-DE	An exploratory clinical study to investigate mavrilimumab, an antibody being developed for the treatment of moderate to severe rheumatoid arthritis, an inflammatory condition that affects the joints versus a different antibody whose mechanism works by inh
EUCTR2011-006001-10-IT	Efficacy of rituximab at the dose of 500 mg e.v., two infusions two weeks apart, versus rituximab at the usual dose of 1000 mg, two infusions two weeks apart, in patients affected by rheumatoid arthritis, who had been previously treated with rituximab at the standard dose for at least two cycles obtaining a good clinical response
EUCTR2011-006040-79-DK	A clinical trial with the aim to explore the efficacy and safety of adding tocilizumab to standard of care in patients with early rheumatoid arth - please add missing text
EUCTR2011-006125-14-HU	A multicenter, open-label, single arm, long term extension study of WA19926 to describe safety during treatment with tocilizumab in patients with early, moderate to severe rheumatoid arthritis - function LTE
EUCTR2012-000139-21-AT	Multi-center biomarker trial to predict therapeutic responses of patients with rheumatoid arthritis to a specific biologic mode of action
EUCTR2012-001760-30-IT	Evaluation effects of treatment with an inhibitor of the receptor of a protein (interleukin-6 il-6)involved in inflammatory process, on the clinical response and on the changes from baseline in the biomarkers in patients with rheumatoid arthritis (RA)not responding adequately to disease-modifying antirheumatic drugs (DMARDs) and/or to a first biological agent.

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EUCTR2012-002009-23-HU	Clinical trial to demonstrate that treatments with gp2015 and Enbrel® are comparable in patients with rheumatoid arthritis
EUCTR2012-002322-73-HU	A phase 3 study in moderate to severe rheumatoid arthritis
EUCTR2012-002535-28-GB	A randomised, open labelled study in anti-TNFa inadequate responders to investigate the mechanisms for response - resistance to rituximab versus tocilizumab in RA (r4-ra) - r4-ra
EUCTR2012-003057-29-CZ	A multi-centre, randomised, double-blind multiple dose study of increasing doses of xmab5871 in patients with rheumatoid arthritis.
EUCTR2012-003194-25-LT	Bioequivalence trial of Mabioncd20® (Mabion SA) compared to reference product: Mabthera® (rituximab, Roche) in patients with rheumatoid arthritis
EUCTR2012-003536-23-CZ	To evaluate the safety of sar153191 (REGN88) and tocilizumab added to other RA drugs in patients with RA who are not responding to or intolerant of anti-TNF therapy (Saril-RA-Ascertain)
EUCTR2012-003644-71-ES	Randomized, double-blind, placebo-controlled trial of etanercept plus methotrexate in monoclonal antibody (MAB) anti-TNF failure
EUCTR2012-003876-38-DE	Clinical study to find out if the biologically similar medicine gp2013 is safe in patients with rheumatoid arthritis who have been treated with Rituxan® or Mabthera® in the past
EUCTR2012-004482-40-ES	Evaluation of a protocol for the reduction of doses in patients with rheumatoid arthritis (RA) in clinical remission in treatment with biological therapies
EUCTR2012-005026-30-HU	A study comparing SB4 to Enbrel® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
EUCTR2012-005275-14-NO	Remission in rheumatoid arthritis – assessing withdrawal of disease-modifying antirheumatic drugs
EUCTR2012-005733-37-CZ	A study comparing SB2 to Remicade® in subjects with moderate to severe rheumatoid arthritis
EUCTR2013-000337-13-DE	Prediction of response to certolizumab pegol treatment with MRI of the brain. A multi-center, randomized double-blind controlled study prediction of response to certolizumab-pegol in rheumatoid arthritis (PRECEPRA)
EUCTR2013-000342-19-NL	A clinical trial where patients with rheumatoid arthritis are treated with the study drug tocilizumab, subcutaneous (injection in the skin), with or without other non-biological anti-rheumatic drugs, to study the safety and efficacy of the drug.
EUCTR2013-000525-31-GB	A randomized, double-blind, phase 3 Study of ABP 501 efficacy and safety compared to adalimumab in subjects with moderate to severe rheumatoid arthritis
EUCTR2013-001569-17-IT	A national, open-label, single-arm, phase IIIb study to evaluate the efficacy of weekly tocilizumab subcutaneous, administered as monotherapy or in combination with other non-biological medicinal products in rheumatoid arthritis (RA) patients.
EUCTR2013-002007-34-FI	Safety and efficacy study of tocilizumab injected under the skin in patients with active rheumatoid arthritis (RA) and inadequate response to disease modifying antirheumatic drugs.
EUCTR2013-002150-79-BE	A study to evaluate the efficacy and safety of tocilizumab subcutaneous in RA patients
EUCTR2013-002429-52-ES	Study to evaluate the efficacy, safety and tolerability of subcutaneous (SC) tocilizumab (TCZ) in subjects with rheumatoid arthritis

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EUCTR2013-002777-22-GB	Targeted Ultrasound in Rheumatoid Arthritis (TURA)
EUCTR2013-003177-99-SE	A clinical study to evaluate the safety of two different doses of tofacitinib for the treatment of rheumatoid arthritis.
EUCTR2013-003413-18-GB	Arthritis prevention with abatacept
EUCTR2013-004051-20-ES	Not controlled study to assess the efficacy of tocilizumab in patients with moderate or severe rheumatoid arthritis who are candidates to be treated with a biological therapy as monotherapy
EUCTR2013-004148-49-LT	Randomized study of pf-06438179 and infliximab in combination with methotrexate in subjects with moderately to severely active rheumatoid arthritis
EUCTR2013-004555-21-AT	A randomized, controlled, double-blind, parallel-group, phase 3 study to compare the pharmacokinetics, efficacy and safety between ct-p10, Rituxan and Mabthera in patients with rheumatoid arthritis
EUCTR2013-005543-90-HU	A randomized, double-blind study to compare pharmacokinetics and pharmacodynamics, efficacy and safety of ABP 798 with rituximab in subjects with moderate to severe rheumatoid arthritis
EUCTR2014-000109-11-DE	Study to assess the efficacy and safety of FKB327 compared with Humira®, when each is administered in combination with methotrexate in patients with rheumatoid arthritis
EUCTR2014-000110-61-CZ	Study to assess the long-term efficacy and safety of FKB327 compared with Humira®, when each is administered in combination with methotrexate in patients with rheumatoid arthritis
EUCTR2014-002374-36-SE	A study with dose de-escalation of conventional or biologic treatments in early rheumatoid arthritis in patients with low disease activity.
EUCTR2014-002945-23-GB	A 24-week randomized, open-label, parallel-group, active-controlled, exploratory, proof-of-mechanism imaging study investigating the efficacy of 150 mg of namilumab administered subcutaneously vs adalimumab in patients with moderate to severe early rheumatoid arthritis inadequately responding to methotrexate - a phase 2 study of namilumab vs anti-tumor necrosis factor in patients with rheumatoid arthritis
EUCTR2014-003255-54-CZ	A study evaluating the effects of rgb-03 and Mabthera combined with methotrexate in patients with rheumatoid arthritis
EUCTR2014-003307-30-HU	Multiple dose study of ucb4940 as add-on to certolizumab pegol in subjects with rheumatoid arthritis
EUCTR2014-003453-34-EE	Study of a new drug's effect in people with rheumatoid arthritis who have not responded sufficiently well to treatment with methotrexate.
EUCTR2014-003529-16-GB	Stratification of biologic therapies for rheumatoid arthritis by pathobiology
EUCTR2014-004558-33-Outside-EU/EEA	A multicenter, open-label study of the safety, efficacy, and pharmacokinetics of the human anti-TNF monoclonal antibody adalimumab in children with polyarticular juvenile rheumatoid arthritis
EUCTR2014-004673-16-DE	Randomized, blinded, controlled study to compare the efficacy of treatment with tocilizumab with or without glucocorticoids in rheumatoid arthritis.
EUCTR2014-004704-29-ES	This trial is designed to determine what effects the human body has on the investigational medicine, ABP 710, and what effects the body has on the investigational medicine after you have been given it, and if this is comparable to what is seen for the licensed medicine, infliximab, in patients

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	with moderate or severe rheumatoid arthritis (RA). This study will assess if the investigational medicine is safe and effective in treating moderate or severe RA compared to the licensed medicine.
EUCTR2014-004868-38-GR	A study comparing the use of etanercept and methotrexate, used either alone or in combination, for maintaining remission in rheumatoid arthritis.
EUCTR2014-004904-31-NL	A clinical study to investigate the infliximab serum concentration of Remsima™ (infliximab biosimilar) after switching from Remicade (infliximab) in subjects with Crohn's disease (CD), ulcerative colitis (UC) or rheumatoid arthritis (RA) in stable remission.
EUCTR2014-005368-13-HU	A study comparing sait101 to Mabthera® or Rituxan® in patients with rheumatoid arthritis (RA)
EUCTR2015-000581-58-CZ	A randomized,biomarker trial to predict therapeutic responses of patients with rheumatoid arthritis to a specific biologic mode of action
EUCTR2015-001246-28-BE	Ultrasound scores as imaging biomarkers of early response to subcutaneous tocilizumab in association with methotrexate in early rheumatoid arthritis (TOVERA study)
EUCTR2015-001894-41-HU	Multicenter study to evaluate efficacy and safety of certolizumab pegol in subjects with active inflammation in the spine with no damage on x-rays.
EUCTR2015-002284-42-FI	The rationale for this study is to gain insight in the extent and impact of immunogenicity of TNF inhibitors in the European daily clinical practice. Furthermore, an European wide database will give insight in factors influencing immunogenicity and treatment outcome in terms of disease activit
EUCTR2015-002466-22-Outside-EU/EEA	A randomized, multi-center, blinded, placebo-controlled study with an openlabel run-in period to evaluate the efficacy, safety, and pharmacokinetics of daily, single, subcutaneous injections of r-methuil-1ra (anakinra) in polyarticular-course juvenile rhe
EUCTR2015-002809-12-HU	A study to compare ylb113 and Enbrel for the treatment of rheumatoid arthritis
EUCTR2015-003433-10-CZ	ADMYRA Trial: clinical trial to compare treatment with GP2017 and Humira® in patients with rheumatoid arthritis
EUCTR2015-004386-91-PL	Study to explore and compare the effects of a new drug in combination with methotrexate therapy in people with early and established rheumatoid arthritis.
EUCTR2015-004858-17-NL	Remission induction in very early rheumatoid arthritis
EUCTR2015-005307-83-CZ	Study of the efficacy and safety of Olokizumab in patients with moderately to severely active rheumatoid arthritis inadequately controlled by methotrexate therapy
EUCTR2016-000933-37-HU	Study to compare abt-494 to abatacept in subjects with rheumatoid arthritis on stable dose of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) who have an inadequate response or intolerance to biologic DMARDs (select-choice)
EUCTR2016-002125-11-LV	Evaluating efficacy, pharmacokinetics and safety between subcutaneous CT-P13 and intravenous CT-P13 in patients with active rheumatoid arthritis
EUCTR2016-002852-26-HU	MSB11022 in moderately to severely active rheumatoid arthritis
EUCTR2016-002908-15-NL	Redo study: research into the effects of lower doses rituximab in patients with rheumatoid arthritis
IRCT201206266302N3	Comparative analysis of Altebrel® (aryogen) with Enbrel®
IRCT2014090319025N1	Efficacy of Mabasia (adalimumab) in rheumatoid arthritis
IRCT2015030321315N1	The effect of adalimumab on treatment of rheumatoid arthritis

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ISRCTN14909030	Rituximab in rheumatoid arthritis: is a reduced dose every 6 months equally effective as the regular dose if the patient has low or very low disease activity?
ISRCTN15819795	Effect of anakinra (soluble interleukin-1 receptor antagonist) as combination therapy: second uk combination therapy in early rheumatoid arthritis
ISRCTN23348591	A placebo controlled study of the effect of extended treatment with rituximab on resistant rheumatoid arthritis: clinical and radiological outcomes
ISRCTN27093749	Rituximab in rheumatoid arthritis in patients who failed therapy with tumour necrosis factor-blockers: a multi-centre clinical observational real-life study (phase IIIb)
ISRCTN29665463	A placebo-controlled trial of anti-TNFa chimeric monoclonal antibody (infliximab, Remicade) in the modification of vascular disease markers in active rheumatoid arthritis
ISRCTN36745608	A controlled randomised double-blind multicentre study comparing two therapy strategies in disease modifying anti-rheumatic drug-naive early rheumatoid arthritis patients over 48 weeks: induction therapy with adalimumab and methotrexate over 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate monotherapy
ISRCTN39045408	Anti-tumour necrosis factor (anti-TNF) therapy over two years increases body fat mass in early rheumatoid arthritis
ISRCTN44880063	Differentiating the mechanism of action of anti-TNF alpha agents
ISRCTN46017566	Arthritis prevention in the pre-clinical phase of rheumatoid arthritis with abatacept
ISRCTN48638981	A multicentre randomised double-blind placebo-controlled study comparing two regimens of combination induction therapy in early disease-modifying anti-rheumatic drug naïve rheumatoid arthritis
ISRCTN49682259	Remission induction in very early rheumatoid arthritis: a comparison of etanercept plus methotrexate plus steroid with standard therapy
ISRCTN51200229	Randomised double blind trial of safety of anti-tumour necrosis factor (anti-TNF) chimeric monoclonal antibody (infliximab) in combination with methatrexate compared to methatrexate alone in patients with rheumatoid arthritis on standard disease modifying anti-rheumatic drugs
ISRCTN57761809	Effect of anti-tumour necrosis factor alpha (TNFa) therapy on blood vessel health in patients with rheumatoid arthritis
ISRCTN62900439	Leflunomide or methotrexate plus subcutaneous tumour necrosis factor-alpha (TNF-alpha) blocking agents in rheumatoid arthritis
ISRCTN70800019	Effects on tocilizumab drug therapy on fat tissue proteins in rheumatoid arthritis
ISRCTN75505683	Remission induction study in early rheumatoid arthritis (RA)
ISRCTN82317088	Changes in bone density and bone turnover in patients with rheumatoid arthritis treated with rituximab, a b cell depleting antibody
ISRCTN89222125	Switching to alternative tumour-necrosis factor (TNF)-blocking drugs or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-blocking drug
ISRCTN95861172	Randomised efficacy and discontinuation study of etanercept and adalimumab (RED SEA): A pragmatic open label study in rheumatoid arthritis

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ISRCTN97686858	A randomized, controlled study of intra-articular injections of etanercept or glucocorticosteroids in patients with rheumatoid arthritis
JPRN-JapicCTI-111620	A randomized, double-blind, phase I/II study of CT-P13 compared with Remicade in patients with rheumatoid arthritis
JPRN-JapicCTI-142505	Phase III study of MRA-SC 162 mg/week
JPRN-JapicCTI-142621	Chs-0214 phase III trial
JPRN-UMIN000000512	Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with infliximab and methotrexate
JPRN-UMIN000001240	The efficacy of tocilizumab to patients with rheumatoid arthritis refractory to anti-TNF agents: the open trial
JPRN-UMIN000001407	The efficacy and safety of the new biologic agents (humanized anti-human interlukin-6 receptor monoclonal antibody) on abnormal lipid metabolism and atherosclerosis for rheumatoid arthritis patients in Japan
JPRN-UMIN000001798	Prevention of cartilage destruction in rheumatoid arthritis by etanercept (PRECEPT study)
JPRN-UMIN000002110	Discontinuation of infliximab therapy after acquisition of low disease activity by infliximab in rheumatoid arthritis study: RRR (remission induction by Remicade) study
JPRN-UMIN000002246	Study for predictors of effectiveness in tocilizumab therapy (PETITE)
JPRN-UMIN000002340	Comparison of effects between higher dosages of infliximab and switching to other biologics for rheumatoid arthritis patients with less responsiveness to infliximab therapy (Chamlet)
JPRN-UMIN000002421	Multicenter, open-label parallel-groups study comparing tocilizumab versus conventional treatment in rheumatoid arthritis with the complication of aa amyloidosis
JPRN-UMIN000002687	Enbrel clinical outcome in RA patients for growing evidence
JPRN-UMIN000002744	Success of tocilizumab in RA patients with remission induction and sustained efficacy after discontinuation
JPRN-UMIN000003344	Induction of the remission by use of infliximab in RA
JPRN-UMIN000003880	Keeping cartilagious quality by adalimumab in patient with rheumatoid arthritis in Kansai area
JPRN-UMIN000004412	Corticosteroid-sparing effect of Actemra in patients with rheumatoid arthritis refractory to anti-TNF agents, methotrexate and corticosteroid
JPRN-UMIN000005113	Evaluation of the clinical remission and its sustainment after discontinuation of infliximab in patients with rheumatoid arthritis who receive "programmed" treatment in randomized controlled trial
JPRN-UMIN000005590	Maintenance of remission by tocilizumab mono-therapy after remission obtained by combination with methotrexate in patients with rheumatoid arthritis
JPRN-UMIN000006914	Postmarketing surveillance for investigating success in achieving clinical and functional remission and sustaining efficacy with tocilizumab in biologics naive RA patients
JPRN-UMIN000006956	Efficacy and safety of tocilizumab in RA patients in daily clinical practice: an retrospective observational study

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JPRN-UMIN000007019	Efficacy and safety of tocilizumab mono-therapy in patients with adult-onset still's disease
JPRN-UMIN000007086	An observational study for investigating success in achieving clinical, structural and functional remission and sustaining efficacy with tocilizumab
JPRN-UMIN000007380	Comparison of the effects of single high-dose methotrexate and methotrexate-tocilizumab therapy on rheumatoid arthritis
JPRN-UMIN000007432	Prospective research of infliximab treatment in active RA patients refractory to anti-interleukin six receptor monoclonal antibody.
JPRN-UMIN000007539	Follow-up study of patients with rheumatoid arthritis who treated infliximab for 1 year and did not reach a clinical remission in rrrr study
JPRN-UMIN000007786	"Effect examination of infliximab to the effect insufficient example and the example of effect decrease of the 1st TNF inhibitor in rheumatoid arthritis "
JPRN-UMIN000007806	The feasibility study of accelated infliximab infusion during maintenance phase
JPRN-UMIN000008185	Pilot study on the efficacy and safety of low-dose tocilizumab therapy in elderly RA patients
JPRN-UMIN000008281	Dose-escalation study of infliximab or methotrexate based on the disease activity in patients with rheumatoid arthritis treated with infliximab
JPRN-UMIN000008404	Extension of tocilizumab dose intervals in patients with low to moderate disease activity rheumatoid arthritis using il-6 serum level as starting criteria.
JPRN-UMIN000008572	The kitasato institute non-inferiority trial of etanercept and tacrolimus ,the combined therapy with methotrexate in rheumatoid arthritis patients
JPRN-UMIN000008756	Abatacept-based approach to cure of RA
JPRN-UMIN000008812	Efficacy and safety of tocilizumab mono-therapy in patients with large vessel vasculitis (lvv; giant cell arteritis or takayasu arteritis) and polymyalgia rheumatica (pmr)
JPRN-UMIN000008889	Cohort study of infectious disease risk management in rheumatoid arthritis patients receiving tocilizumab
JPRN-UMIN000009425	A validity inspection study of the treat-to-target strategy with golimumab for the treatment of rheumatoid arthritis patient
JPRN-UMIN000009435	Analysis of factors for bio-free remission due to the tight control by Remicade in rheumatoid arthritis patients. Birdie study
JPRN-UMIN000009887	Associations between the initial concentration of serum TNF alpha and effects due to increasing a dose of infliximab, and between effects of infliximab and the concentration of serum il-6
JPRN-UMIN000010033	To investigate the efficacy of tocilizumab in RA patients with moderate disease activity under biologic therapy
JPRN-UMIN000011520	Keep persistent efficacy by Abstaining from biological treatment after numerical SDAI remission with adalimumab (KANSAI study)
JPRN-UMIN000011584	A longitudinal, prospective, multicenter observational study in patients with rheumatoid arthritis receiving tocilizumab

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JPRN-UMIN000012005	Identification of bio-markers predicting the therapeutic effects of tocilizumab in rheumatoid arthritis
JPRN-UMIN000012073	Effects of subcutaneous actemura and MTX blending in RA
JPRN-UMIN000012306	Observational study for investigating the ability of recuperation of work/ house work state with tocilizumab (Actemra) subcutaneous treatment in biologics-naive RA patients
JPRN-UMIN000012690	Study of actemura remission induction of RA and sequential maintenance of remission by reasonable cost treatment
JPRN-UMIN000013750	Study on effects of cytokine targeted therapy on periodontal condition in patients with rheumatoid arthritis
JPRN-UMIN000014311	Examination of the clinical remission and functional remission in infliximab using the increase-in-quantity protocol to TNF-alpha inhibitory drug resistance rheumatoid arthritis
JPRN-UMIN000014484	Saitama Actemra study for QoL in patients with rheumatoid arthritis
JPRN-UMIN000014670	The effect of tocilizumab on synovitis of rheumatoid arthritis. Analysis by musculoskeletal ultrasonography
JPRN-UMIN000014934	A study for effectiveness and safety of tocilizumab therapy in rheumatoid arthritis patients with renal insufficiency.
JPRN-UMIN000015175	Head-to-head comparison of subcutaneous tocilizumab versus abatacept for rheumatoid arthritis : prospective, randomized trial.
JPRN-UMIN000015297	The feasibility study of accelerated infliximab infusion from initial administration
JPRN-UMIN000015482	Maintenance of remission with 6-week interval of tocilizumab in RA patients who have been in remission
JPRN-UMIN000015616	Biologic mater clinical performance test for ADA and TCZ efficacy prediction
JPRN-UMIN000016844	The clinical study for seeking strategy how to treat rheumatoid arthritis by TNF inhibitors
JPRN-UMIN000016950	Clinical outcome in patients with rheumatoid arthritis switched to tumor necrosis factor blockers after tocilizumab or abatacept
JPRN-UMIN000017230	Correlation between efficacy of the biological therapy (tocilizumab) and levels of oxidative stress markers in Japanese patients with rheumatoid arthritis (inadequate responders to existing therapies)
JPRN-UMIN000017495	Establish the suitable strategy of maintenance therapy for rheumatoid arthritis patient with methotrexate and adalimumab
JPRN-UMIN000017577	Tapering and withdrawal of methotrexate(MTX) or tocilizumab(TCZ), after achievement of RA remission in concomitant use of MTX and TCZ,a randomized control study.
JPRN-UMIN000017947	Efficacy and change of serum il-6 levels in patients with rheumatoid arthritis treated with tocilizumab
JPRN-UMIN000018659	Inhibitory effects of tocilizumab on serum oxidative stress in patients with rheumatoid arthritis - comparison with other biologic agents-
JPRN-UMIN000020799	Efficacy of infliximab as a second bio in patients with refractory rheumatoid arthritis

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JPRN-UMIN000020833	The efficacy of iguratimod, and adding adalimumab in patients with active rheumatoid arthritis: an open label multicenter randomized parallel study
JPRN-UMIN000021004	Effectiveness and safety of tocilizumab therapy for rheumatoid arthritis patients
JPRN-UMIN000021048	Longitudinal study about the impact of treatment with tumor necrosis factor (TNF) inhibitors on tuberculin skin test (tst) reaction in patients with rheumatoid arthritis (RA).
JPRN-UMIN000021247	Tocilizumab treatment with reducing and stopping methotrexate in patients with rheumatoid arthritis in stable low disease activity-state
JPRN-UMIN000021492	To investigate the safety of switch from infliximab biosimilar 1 in rheumatoid arthritis patients.
JPRN-UMIN000021929	Optimization of infliximab withdrawal strategy for rheumatoid arthritis
JPRN-UMIN000023006	Usefullness of infliximab as a second tumor necrosis factor inhibitor in patients with rheumatoid arthritis with inadequate response to tumor necrosis factor inhibitor
JPRN-UMIN000024025	The clinical impact of methotrexate dose reduction at combination therapy with adalimumab plus methotrexate in rheumatoid arthritis; ALIBABA study
JPRN-UMIN000024071	Serious infections after tocilizumab administration in patients with rheumatoid arthritis: a retrospective study using an adverse drug reaction database -analysis of clinical symptoms and laboratory test data in serious infections-
KCT0000089	Identification of the best treatment strategy in Korean patients with early rheumatoid arthritis
NCT00000433	Blocking tumor necrosis factor in ankylosing spondylitis
NCT00001862	Tnrf:fc to treat eye inflammation in juvenile rheumatoid arthritis
NCT00001901	Etanercept to treat Wegener's granulomatosis
NCT00001954	Etanercept therapy for Sjögren's syndrome
NCT00006070	Etanercept (Enbrel) to treat pain and swelling after third molar extraction
NCT00006292	Infliximab for the treatment of early rheumatoid arthritis
NCT00012506	The safety and efficacy of a tumor necrosis factor receptor fusion protein on uveitis associated with juvenile rheumatoid arthritis
NCT00029042	Infliximab to treat children with juvenile rheumatoid arthritis
NCT00034060	The role of cytokines on growth hormone suppression in premenopausal women with rheumatoid arthritis and the effect of treatment with etanercept
NCT00036374	A study of the safety and effectiveness of infliximab (Remicade) in patients with juvenile rheumatoid arthritis
NCT00036387	A study of the safety and effectiveness of infliximab (Remicade) in patients with rheumatoid arthritis.
NCT00037648	Juvenile rheumatoid arthritis
NCT00037700	Evaluation of the efficacy of combination treatment with anakinra and pegsunercept in improving rheumatoid arthritis

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NCT00048568	A phase III study of abatacept (BMS-188667) in patients with active rheumatoid arthritis and inadequate response to methotrexate
NCT00048581	Phase III study of BMS-188667 (CTLA4IG) in patients with rheumatoid arthritis who are currently failing anti-TNF therapy or who have failed anti-TNF therapy in the past.
NCT00048932	A phase III study of bms-188667 in subjects with active rheumatoid arthritis
NCT00069329	Anakinra to treat patients with neonatal onset multisystem inflammatory disease
NCT00074438	Study to assess the efficacy and safety of rituximab in patients with rheumatoid arthritis
NCT00075075	Infliximab to treat non-infectious scleritis
NCT00078806	Safety and efficacy study of etanercept (Enbrelâ®) in children with systemic onset juvenile rheumatoid arthritis
NCT00094341	Preference of rheumatoid arthritis (RA) patients of Enbrel® (etanercept) auto-injector versus Enbrel® pre-filled syringes
NCT00094900	Interleukin-1 trap to treat autoinflammatory diseases
NCT00095147	Abatacept and infliximab in combination with methotrexate in subjects with rheumatoid arthritis
NCT00095173	BMS-188667 in children and adolescents with juvenile rheumatoid arthritis
NCT00101829	Anti-CD20 antibody therapy for Sjögren's syndrome
NCT00106522	A study to assess the effect of tocilizumab + methotrexate on signs and symptoms in patients with moderate to severe active rheumatoid arthritis currently on methotrexate therapy
NCT00106535	A study to assess the effect of tocilizumab + methotrexate on prevention of structural joint damage in patients with moderate to severe active rheumatoid arthritis (RA)
NCT00106548	A study to assess the effect of tocilizumab + methotrexate on signs and symptoms in patients with moderate to severe active rheumatoid arthritis
NCT00106574	A study to assess the effect of tocilizumab + DMARD therapy on signs and symptoms in patients with moderate to severe active rheumatoid arthritis
NCT00109408	A study to assess the safety and efficacy of tocilizumab in patients with active rheumatoid arthritis
NCT00111410	Evaluating the effect of anakinra (r-methuil-1ra) on vaccine antibody response in subjects with rheumatoid arthritis (RA)
NCT00115219	Evaluating efficacy and safety of etanercept 50 mg twice weekly (biw) in rheumatoid arthritis (RA) subjects who are sub-optimal responders to etanercept 50 mg once weekly (qw)
NCT00121043	Evaluating Kineretâ® (anakinra) in rheumatoid arthritis (RA) subjects using aself-reported questionnaire
NCT00122382	Remission and joint damage progression in early rheumatoid arthritis
NCT00124449	Study of abatacept versus placebo to assess the prevention of rheumatoid arthritis (RA) in adult patients
NCT00132418	Study of Enbrel in rheumatoid arthritis (RA) subjects with comorbid disorders

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NCT00135720	Study of etanercept (Enbrel) in the treatment of pemphigus vulgaris
NCT00144508	Phase III comparative study(open-label) of MRA for rheumatoid arthritis(RA)
NCT00144521	Comparative study (double-blind) of MRA for rheumatoid arthritis (RA)
NCT00144560	Drug-drug interaction study of MRA in patient with rheumatoid arthritis (RA)
NCT00152386	A placebo controlled study to assess efficacy and safety of certolizumab pegol in the treatment of rheumatoid arthritis
NCT00160602	A study of liquid certolizumab pegol as additional medication to methotrexate in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis
NCT00160641	A study of the safety and effectiveness of liquid certolizumab pegol in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis
NCT00160693	Open label long-term safety study of certolizumab pegol (CZP) for patients with rheumatoid arthritis
NCT00162266	Abatacept with methotrexate- phase IIb
NCT00162279	The study of abatacept in combination with etanercept
NCT00175877	A study of the safety and effectiveness of lyophilized certolizumab pegol in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis
NCT00195494	Study comparing etanercept and methotrexate vs. Methotrexate alone in rheumatoid arthritis
NCT00195663	Efficacy and safety of adalimumab and methotrexate (MTX) versus MTX monotherapy in subjects with early rheumatoid arthritis
NCT00195702	Efficacy and safety of adalimumab in patients with active rheumatoid arthritis treated concomitantly with methotrexate
NCT00202852	A placebo-controlled, double-blinded, randomized trial of Remicade in Korean patients with rheumatoid arthritis despite methotrexate (study p04280)(completed)
NCT00207714	An efficacy and safety study of CNTO 148 subcutaneous injection compared with placebo in patients with active rheumatoid arthritis
NCT00216177	Comparison of adalimumab and infliximab treatment of rheumatoid arthritis
NCT00228839	Gvh 022p: study using anti tumor necrosis factor antibody (infliximab) for treatment of acute graft versus host disease
NCT00233558	Open-label steroid reduction study of adalimumab with methotrexate in patients with active rheumatoid arthritis
NCT00234845	Adalimumab in combination with methotrexate vs methotrexate alone in early rheumatoid arthritis
NCT00234897	Efficacy of Humira in subjects with active rheumatoid arthritis

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NCT00234936	Quality of life study with adalimumab in rheumatoid arthritis
NCT00235859	Adalimumab administered in Korean rheumatoid arthritis subjects treated with methotrexate
NCT00236028	A safety and efficacy study for infliximab (Remicade) with methotrexate in patients with early rheumatoid arthritis
NCT00243412	A study of the safety and efficacy of rituximab in patients with moderate to severe rheumatoid arthritis receiving methotrexate
NCT00244556	Study comparing Enbrel (etanercept) plus methotrexate versus Enbrel alone in active rheumatoid arthritis despite current methotrexate therapy
NCT00249041	Enbrel liquid immunogenicity protocol
NCT00252668	Study evaluating the combination of etanercept and methotrexate in rheumatoid arthritis subjects
NCT00254293	Study to assess steady-state trough concentrations, safety, and immunogenicity of abatacept after subcutaneous (sc) administration to subjects with rheumatoid arthritis (RA)
NCT00259610	Treatment of early aggressive rheumatoid arthritis (TEAR)
NCT00261118	Rituximab in active ulcerative colitis
NCT00264537	A study of the safety and efficacy of golimumab in subjects with rheumatoid arthritis that are methotrexate-naive
NCT00264550	An efficacy and safety study of golimumab in patients with active rheumatoid arthritis despite methotrexate therapy
NCT00266227	A study of retreatment with rituximab in patients with rheumatoid arthritis receiving background methotrexate
NCT00269867	Infliximab plus methotrexate for the treatment of rheumatoid arthritis
NCT00279734	Vaccination study of abatacept (BMS-188667) for normal healthy volunteers
NCT00279760	Phase I/II multiple-dose LEA29Y vs CTLAG4IG vs placebo in rheumatoid arthritis
NCT00282308	A study to evaluate the effects of rituximab on immune responses in subjects with active rheumatoid arthritis receiving background methotrexate
NCT00283712	Use of infliximab for the treatment of pemphigus vulgaris
NCT00291915	Multicenter randomized prospective trial comparing methotrexate alone or in combination with adalimumab in early arthritis
NCT00293202	Safety and efficacy study of the effect of etanercept in hemodialysis patients
NCT00298272	Safety and tolerability of Rituxan With methotrexate and etanercept or methotrexate and adalimumab in patients with active rheumatoid arthritis
NCT00299104	A study to evaluate rituximab in combination with methotrexate in methotrexate-naive patients with active rheumatoid arthritis
NCT00299130	A study to evaluate the safety and efficacy of rituximab in combination with methotrexate compared to methotrexate alone in patients with active rheumatoid arthritis

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NCT00299546	A study of the safety and efficacy of golimumab (CNTO 148) in subjects with active rheumatoid arthritis previously treated with biologic anti-TNFa agent(s)
NCT00317538	Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after incomplete response to etanercept
NCT00327275	The effects of a 16-week individualized, intensive strength training program in patients with rheumatoid arthritis
NCT00345748	A study of abatacept in Japanese patients with active rheumatoid arthritis while receiving methotrexate
NCT00361335	A study of safety and effectiveness of golimumab in participants with active rheumatoid arthritis despite methotrexate therapy
NCT00363350	Rituximab treatment in Sjögren's syndrome
NCT00365001	A drug interaction study between tocilizumab, methotrexate and simvastatin on patients with rheumatoid arthritis.
NCT00393471	Study comparing etanercept plus methotrexate to either etanercept or methotrexate alone in rheumatoid arthritis.
NCT00394589	Re³ (re-cube: retain Remicade® response)(study P04249AM3)
NCT00396747	A comparison of methotrexate alone or combined to infliximab or to pulse methylprednisolone in early rheumatoid arthritis: a magnetic resonance imaging study
NCT00396812	Rituximab for the treatment of early rheumatoid arthritis (RA)
NCT00405275	Rheumatoid arthritis: comparison of active therapies in patients with active disease despite methotrexate therapy
NCT00409838	A phase III study of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate
NCT00420199	A phase IIIb study of BMS-188667 in subjects with active rheumatoid arthritis and inadequate response to methotrexate
NCT00420927	Study of the optimal protocol for methotrexate and adalimumab combination therapy in early rheumatoid arthritis
NCT00422227	Study comparing etanercept with usual DMARD therapy in subjects with rheumatoid arthritis in the Asia Pacific region
NCT00422383	A study of retreatment with Mabthera (rituximab) in combination with methotrexate in patients with rheumatoid arthritis (RA)
NCT00424502	A study of Mabthera (rituximab) in patients with rheumatoid arthritis who have had an inadequate response to a TNF-blocker.
NCT00425932	Impact of rituximab on MRI evidence of disease activity in patients with moderate to severe rheumatoid arthritis
NCT00426543	Effect of b-cell depletion in patients with primary Sjögren's syndrome
NCT00432406	Tumor necrosis factors (TNF)- blockade for psoriatic arthritis

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NCT00442611	A study to evaluate the safety and efficacy of abatacept in patients with diffuse systemic sclerosis (scleroderma)
NCT00443430	Trial of early aggressive drug therapy in juvenile idiopathic arthritis
NCT00443950	Study evaluating the efficacy and safety of etanercept in Chinese subjects with rheumatoid arthritis
NCT00445770	Study evaluating the efficacy and safety of etanercept and methotrexate in Japanese subjects with rheumatoid arthritis
NCT00459706	Study comparing perceptions and satisfaction for two different delivery mechanisms for etanercept
NCT00462072	Centocor microarray study of patients
NCT00463580	A study of infliximab for treatment resistant major depression
NCT00468377	Safety and efficacy study of re-treatment with rituximab (Mabthera/Rituxan) in patients with active rheumatoid arthritis who respond poorly to anti-TNFî± therapies
NCT00468546	A study to evaluate the safety and efficacy of Mabthera (rituximab) in combination with methotrexate (MTX) in participants with active rheumatoid arthritis who failed on anti-tumor necrosis factor alpha therapy
NCT00480272	Prospective study on intensive early rheumatoid arthritis treatment
NCT00484237	A study evaluating 10 mg and 25 mg doses of etanercept in patients with rheumatoid arthritis
NCT00502996	A non-comparative study to assess the safety of Mabthera (rituximab) in patients with rheumatoid arthritis.
NCT00503425	A study of Mabthera (rituximab) in participants with rheumatoid arthritis who have had an inadequate response to disease-modifying antirheumatic drugs (DMARD) and/or anti-tumor necrosis factor (anti-TNF) therapy.
NCT00514982	Medical treatment of colitis in patients with Hermansky-Pudlak Syndrome
NCT00520572	A 6-month randomised, double-blind, open arm comparator, phase IIb, with azd9056, in patients with rheumatoid arthritis (RA)
NCT00521924	Induction of remission in RA patients at low disease activity by additional infliximab therapy (study P04644AM1) (terminated)
NCT00522184	Intra-articular injection of etanercept in patient suffering from rheumatoid arthritis : a double-blind randomized study
NCT00523692	Remission induction in very early rheumatoid arthritis
NCT00531817	A study of tocilizumab in combination with DMARDs in patients with moderate to severe rheumatoid arthritis
NCT00533897	Phase IIIb subcutaneous missed dose study
NCT00534313	Safety and efficacy of abatacept versus placebo in participants with psoriatic arthritis
NCT00535782	A study of the effect of tocilizumab on markers of atherogenic risk in patients with moderate to severe rheumatoid arthritis

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NCT00537667	The spectra study
NCT00538902	Safety and efficacy study of adalimumab in adult Chinese rheumatoid arthritis subjects treated with methotrexate
NCT00544154	Efficacy and safety of CDP870 and methotrexate compared to methotrexate alone in subjects with rheumatoid arthritis
NCT00548834	Efficacy and safety of CDP870 versus placebo in the treatment of the signs and symptoms of rheumatoid arthritis
NCT00550446	A phase 2 study for patients with a physician's diagnosis of rheumatoid arthritis
NCT00555542	An analysis of peripheral blood t cell subsets on rheumatoid arthritis
NCT00559585	Methotrexate-inadequate response study
NCT00565331	Rituximab for prevention of rejection after renal transplantation
NCT00565409	Study comparing etanercept in combination with methotrexate in subjects with rheumatoid arthritis
NCT00578305	A study of rituximab (Mabthera®/Rituxan®) in patients with rheumatoid arthritis and inadequate response to methotrexate
NCT00578565	Rituximab in rheumatoid arthritis lung disease
NCT00580229	A safety analysis of oral prednisone as a pre-treatment for rituximab in rheumatoid arthritis.
NCT00580840	Dosing flexibility study in patients with rheumatoid arthritis
NCT00595413	Atacicept in anti-tumor necrosis factor alpha-naive subjects with rheumatoid arthritis (AUGUST II)
NCT00647270	Study comparing 80 mg of adalimumab with placebo, and demonstrating the non-inferiority of monthly 80 mg adalimumab dosing compared with 40 mg adalimumab every other week dosing
NCT00647491	A study of adalimumab in adult Japanese subjects with rheumatoid arthritis
NCT00647920	Study of adalimumab administered as subcutaneous injections in adult Chinese rheumatoid arthritis subjects treated with methotrexate
NCT00649545	Study of the human anti-TNF monoclonal antibody in patients with active rheumatoid arthritis
NCT00649922	Assessment of the effect of adalimumab on response to influenza virus and pneumococcal vaccines in subjects with rheumatoid arthritis
NCT00650026	Early access program of the safety of human anti-TNF monoclonal antibody adalimumab in subjects with active rheumatoid arthritis
NCT00650156	Pharmacokinetic and safety study with adalimumab in Chinese subjects with mild rheumatoid arthritis
NCT00650390	Open label study to assess efficacy and safety of the fully human anti-TNF-alpha monoclonal antibody adalimumab
NCT00654368	CAMEO: Canadian methotrexate and etanercept outcome study

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NCT00660647	Optimized treatment algorithm for patients with early rheumatoid arthritis (RA)
NCT00664521	Atacicept in combination with rituximab in subjects with rheumatoid arthritis
NCT00674362	Rheumatoid arthritis (RA) moderate to low disease activity study
NCT00678782	Evaluation of the efficacy and safety of intra-articular etanercept in patients with refractory knee joint synovitis
NCT00683345	Fatigue and interleukin-1 (IL-1) blockade in primary Sjögrens syndrome
NCT00686868	Study to evaluate sc route of administration of ofatumumab in RA patients
NCT00688103	Efficacy and safety of etanercept in active RA despite methotrexate therapy in japan
NCT00689728	A study for patients with rheumatoid arthritis on methotrexate (MTX) with an inadequate response to TNF-inhibitor therapy
NCT00691028	Efficacy and safety of increased dose of ta-650(infliximab) in patients with rheumatoid arthritis
NCT00696059	Humira in rheumatoid arthritis - do bone erosions heal?
NCT00706797	Study evaluating efficacy / safety of etanercept + methotrexate compared to usual treatment in moderate RA subjects
NCT00711503	Anti-interleukin-1 in diabetes action
NCT00713544	A proof of concept and dose ranging study in patients with rheumatoid arthritis
NCT00714493	RESTART C0168Z05 rheumatoid arthritis study
NCT00716248	Bucillamine study of holding remission after infliximab dose-off
NCT00717236	Certolizumab pegol for the treatment of patients with active rheumatoid arthritis
NCT00720798	An extension study of tocilizumab (myeloma receptor antibody [MRA]) in patients completing treatment in tocilizumab core studies
NCT00721123	A long-term extension study of tocilizumab (myeloma receptor antibody [MRA]) in patients with rheumatoid arthritis
NCT00727987	A safety and efficacy study of golimumab (CNTO 148) in patients with active rheumatoid arthritis despite methotrexate therapy
NCT00732875	A trial of anti-TNF chimeric monoclonal antibody (CA2) in Korean patients with active rheumatoid arthritis despite methotrexate (extension part)(study P05645)(completed)
NCT00740948	Tolerance and efficacy of rituximab in Sjögren's disease
NCT00753454	Open label extension for patients coming from the dosing flexibility study in patients with rheumatoid arthritis (RA)
NCT00754559	A study to assess efficacy with respect to clinical improvement in disease activity and safety of tocilizumab in patients wtih active rheumatoid arthritis.
NCT00764725	Comparison of MTX+anti-TNF to MTX+conventional DMARDs in patients with early rheumatoid arthritis (RA) who failed MTX alone (SWEFOT)

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NCT00768053	Evaluation of eular-raid score in rheumatoid arthritis patients
NCT00771251	A safety and efficacy study of golimumab (CNTO148) in patients with active rheumatoid arthritis (RA)
NCT00773461	A study of tocilizumab in combination with DMARD therapy in patients with active rheumatoid arthritis.
NCT00780793	Spacing of TNF-blocker injections in rheumatoid arthritis study
NCT00783536	A multicenter study to compare the efficacy and safety of the combination of etanercept and methotrexate in treatment of rheumatoid arthritis
NCT00789724	Anakinra to prevent post-infarction remodeling
NCT00791921	Efficacy confirmation trial of CDP870 without coadministration of methotrexate (MTX) in Japanese rheumatoid arthritis (RA)
NCT00791999	Efficacy confirmation trial of CDP870 as add-on medication to methotrexate (MTX) in Japanese rheumatoid arthritis (RA)
NCT00794898	Efficacy of Remicade in the treatment of active rheumatoid arthritis despite methotrexate (study p03027)
NCT00796705	Switching anti-TNF-alpha agents in rheumatoid arthritis (RA)
NCT00808210	A study to evaluate ocrelizumab in combination with methotrexate compared with infliximab plus methotrexate in patients with active rheumatoid arthritis currently responding inadequately to etanercept or adalimumab
NCT00808509	A pilot study of the feasibility of discontinuation of adalimumab in stable rheumatoid arthritis patients in clinical remission
NCT00810199	A study of tocilizumab and methotrexate treatment strategies (adding tocilizumab to methotrexate versus switching to tocilizumab) in patients with active rheumatoid arthritis with inadequate response to prior methotrexate treatment
NCT00810277	A study of tocilizumab in patients with rheumatoid arthritis who have an inadequate response to current non-biologic DMARDs
NCT00814866	Bone resorption, osteoclastogenesis and adalimumab
NCT00837434	Anti-TNF agents for the treatment of rheumatoid arthritis
NCT00843778	Follow-up of rheumatoid arthritis (RA) moderate to low disease activity study
NCT00844714	Cardiovascular risk markers in patients with rheumatoid arthritis: effect of rituximab therapy
NCT00845832	A study of combination treatment with Mabthera (rituximab) and Roactemra (tocilizumab) versus Roactemra in patients with rheumatoid arthritis with an incomplete response to methotrexate
NCT00848354	Open-label study comparing etanercept to conventional disease modifying antirheumatic drug (DMARD) therapy
NCT00850343	Long-term treatment study of certolizumab pegol without coadministration of methotrexate in Japanese rheumatoid arthritis (RA) patients

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NCT00851318	Long-term treatment study of certolizumab pegol (cdp870) as add-on medication to methotrexate in Japanese rheumatoid arthritis (RA) patients
NCT00853385	A phase 3 study comparing 2 doses of CP-690,550 and the active comparator, Humira (adalimumab) vs. Placebo for treatment of rheumatoid arthritis
NCT00858780	Study comparing the effect on disease activity when reducing or discontinuing etanercept in subjects with RA
NCT00868751	Single patient use of tocilizumab in systemic onset juvenile idiopathic arthritis
NCT00870467	A study of adalimumab in Japanese subjects with rheumatoid arthritis
NCT00887341	A study comparing infusion rates of tocilizumab in patients with moderate to severe rheumatoid arthritis
NCT00891020	A study of tocilizumab in patients with moderate to severe active rheumatoid arthritis who have an inadequate response to or are unable to tolerate biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs)
NCT00901550	The Chinese university of Hong Kong early arthritis study
NCT00908089	Tnf-blocking therapy in combination with disease-modifying antirheumatic drugs in early rheumatoid arthritis
NCT00913458	Study evaluating etanercept plus methotrexate in early rheumatoid arthritis
NCT00920478	Targeting synovitis in early rheumatoid arthritis
NCT00929864	Abatacept versus adalimumab head-to-head
NCT00948610	Sleep and immunity in rheumatoid arthritis : Remicade substudy
NCT00963703	Treatment of TNFa naive patients with poor prognosis rheumatoid arthritis
NCT00965653	A study of subcutaneously administered tocilizumab in patients with rheumatoid arthritis
NCT00973479	An effectiveness and safety study of intravenous golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate therapy
NCT00977106	Torpedo study: a study on rapid effect of tocilizumab in patients with rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs (DMARDs) or anti-TNF
NCT00979771	A study to investigate the ability of GSK706769 to maintain clinical remission after withdrawal of Enbrel in rheumatoid arthritis patients
NCT00989235	Substudy - low dose of abatacept in subjects with rheumatoid arthritis
NCT00993317	A study of cdp870 as add-on meditation to methotrexate (MTX) in patients with rheumatoid arthritis
NCT00993668	Assessing the use of certolizumab pegol in adult subjects with rheumatoid arthritis on the antibody response when receiving influenza virus and pneumococcal vaccines
NCT00996606	A study of tocilizumab in combination with disease-modifying anti-rheumatic drugs (DMARDs) in participants with moderate to severe active rheumatoid arthritis with an inadequate response to DMARDs

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NCT01000441	Rotation or change of biotherapy after first anti-TNF treatment failure for rheumatoid arthritis
NCT01001832	Efficacy, pharmacokinetics, safety, and immunogenicity study of abatacept administered subcutaneously to treat rheumatoid arthritis in Japanese patients
NCT01002781	Efficacy and safety of tocilizumab in adult's still disease
NCT01004432	Golimumab in rheumatoid arthritis participants with an inadequate response to etanercept (ENBREL) or adalimumab (HUMIRA)
NCT01007435	A study of tocilizumab as monotherapy and in combination with methotrexate versus methotrexate in patients with early moderate to severe rheumatoid arthritis
NCT01009879	Human tumor necrosis factor alpha (TNFa)-induced pre-B cell bone marrow emigrants
NCT01010503	A study of tocilizumab with or without methotrexate in patients with rheumatoid arthritis.
NCT01021735	Optimal management of rheumatoid arthritis patients requiring biologic therapy
NCT01033656	Treatment of refractory adult-onset still's disease with anakinra: a randomized study
NCT01034137	A study of tocilizumab and methotrexate in combination or as monotherapy in treatment-naïve patients with early rheumatoid arthritis
NCT01034397	A study of tocilizumab plus non-biological DMARD in patients with moderate to severe rheumatoid arthritis and an inadequate response to non-biological DMARDs
NCT01044498	A study of tocilizumab in combination with an oral contraceptive in patients with rheumatoid arthritis
NCT01072058	Heart function in rheumatoid arthritis and ankylosing spondylitis pre and post-TNF blocker
NCT01086033	A 3-year study following up patients with moderate to severe rheumatoid arthritis treated with Humira in Greece
NCT01088165	The influence of adalimumab on cardiovascular and metabolic risk in psoriasis
NCT01101555	Repeat dose subcutaneous Rhumatoid arthritis efficacy study
NCT01116427	A cooperative clinical study of abatacept in multiple sclerosis
NCT01117129	A study of efficacy of rituximab [Mabthera/Rituxan] in patients with rheumatoid arthritis using magnetic resonance imaging of the hand (RESONAR)
NCT01119859	A study of tocilizumab (roactemra/Actemra) versus adalimumab in patients with rheumatoid arthritis
NCT01120366	Success of tocilizumab in RA patients with remission induction and sustained efficacy after discontinuation
NCT01123070	Tl011 in severe, active rheumatoid arthritis patients
NCT01126541	SMART Study: a study of re-treatment with Mabthera (rituximab) in patients with rheumatoid arthritis who have failed on anti-TNF alfa therapy
NCT01142726	Efficacy and safety study of abatacept subcutaneous plus methotrexate in inducing remission in adults with very early rheumatoid arthritis

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NCT01147341	Can TNF-alpha incomplete secondary responders attain a safe and efficacious response switching to Cimzia
NCT01162421	A Canadian study to evaluate early use of adalimumab after methotrexate failure in early rheumatoid arthritis
NCT01163617	The usability and injection time of the Physiolis syringe and autoinjector in rheumatoid arthritis patients
NCT01163747	A study of the effects of Roactemra/Actemra on vaccination in patients with rheumatoid arthritis on background methotrexate (VISARA)
NCT01173120	Methotrexate - inadequate response device sub-study
NCT01185288	A study to determine the effect of methotrexate (MTX) dose on clinical outcome and ultrasonographic signs in subjects with moderately to severely active rheumatoid arthritis (RA) treated with adalimumab (MUSICA)
NCT01185301	Study to determine the effects of different doses of methotrexate (MTX) when taken with adalimumab in subjects with early rheumatoid arthritis (RA)
NCT01185522	An observational study of the impact of Roactemra/Actemra on fatigue in patients with rheumatoid arthritis (PEPS)
NCT01194414	A study to compare subcutaneous versus intravenous administration of Roactemra/Actemra (tocilizumab) in participants with moderate to severe active rheumatoid arthritis
NCT01197066	Open-label, extension study of CDP870 in patients with rheumatoid arthritis
NCT01197144	Pain modulation in rheumatoid arthritis (RA) - influence of adalimumab
NCT01211834	Efficacy and safety of tocilizumab in combination with DMARDs in patients with moderate to severe rheumatoid arthritis
NCT01212094	Double blind combination of rituximab by intravenous and intrathecal injection versus placebo in patients with low-inflammatory secondary progressive multiple sclerosis (RIVITALISE)
NCT01213017	The effect of certolizumab pegol on MRI synovitis and bone edema in rheumatoid arthritis patients
NCT01216631	Seronegative oligoarthritis of the knee study (SOKS)
NCT01217086	Program evaluating the autoimmune disease investigational drug ct-p13 in RA patients(PLANETRA)
NCT01217814	Effect of sar153191 (regn88) with methotrexate in patients with active rheumatoid arthritis who failed TNF-î± blockers
NCT01221636	Pharmacokinetic study to compare the blood levels of low vs high metal manufacture of abatacept
NCT01225393	A study to evaluate the efficacy and safety of MLTA3698A in combination with a disease-modifying anti-rheumatic drug (DMARD) compared with adalimumab in combination with a DMARD in patients with active rheumatoid arthritis
NCT01232569	A study of Roactemra/Actemra (tocilizumab) given subcutaneously in combination with traditional DMARDs in patients with moderate to severe active rheumatoid arthritis
NCT01235598	Magnetic resonance image verified early response to certolizumab pegol in subjects with active rheumatoid arthritis (RA)

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NCT01242488	Efficacy and safety of CDP6038 in patients with rheumatoid arthritis with an unsuccessful response to anti-tumor necrosis factor (anti-TNF) therapy
NCT01244958	Addition of rituximab to leflunomide in patients with active rheumatoid arthritis
NCT01245361	A 6-months infliximab or placebo study in UA at high risk of RA:clinical,radiological and synovial benefit
NCT01245439	A study of Roactemra/Actemra (tocilizumab) in patients with moderate to severe rheumatoid arthritis
NCT01245452	Study of the response and cardiorespiratory endurance in early RA patients treated with tocilizumab or methotrexate
NCT01248780	Study of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy
NCT01251120	A study of Roactemra/Actemra (tocilizumab) in combination with DMARDs versus current best practice DMARD therapy in patients with rheumatoid arthritis
NCT01255761	A comparison of two assessment tools in predicting treatment success of Cimzia in rheumatoid arthritis subjects
NCT01258712	Study of tocilizumab in combination with methotrexate for treatment of moderate to severe rheumatoid arthritis patients
NCT01264770	Evaluation of efficacy and safety of Fostamatinib monotherapy compared with adalimumab monotherapy in patients with rheumatoid arthritis (RA)
NCT01270035	Efficacy and safety of adalimumab 80 mg every other week with methotrexate
NCT01270087	The effect of adalimumab (Humira) on vascular abnormalities in rheumatoid arthritis. A pilot study
NCT01270997	Randomized double-blind parallel trial to evaluate equivalence in efficacy and safety of hd203 and Enbrel in RA patients
NCT01272908	A study of Mabthera (rituximab) in patients with rheumatoid arthritis who have failed on one prior anti-TNF therapy (reset)
NCT01274182	Gp2013 in the treatment of RA patients refractory to or intolerant of standard therapy
NCT01283971	A study of Roactemra/Actemra (tocilizumab) versus adalimumab in combination with methotrexate (MTX) in patients with moderate to severe active rheumatoid arthritis and an inadequate response to treatment with only one tumor necrosis factor (TNF)-inhibitor
NCT01292265	A 12 week study to assess changes in joint inflammation using ultrasonography in patients with rheumatoid arthritis (RA)
NCT01295151	SWITCH clinical trial for patients with rheumatoid arthritis who have failed an initial TNF-blocking drug
NCT01295814	Efficacy study of adalimumab to treat interstitial cystitis
NCT01303874	Etanercept and methotrexate in patients to induce remission in early arthritis (empire)
NCT01308255	Infliximab as induction therapy in early rheumatoid arthritis (idea)

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NCT01313208	Moderate rheumatoid arthritis (RA) with etanercept (Enbrel)
NCT01313520	A study to evaluate the effectiveness of infliximab and changes in hand and wrist magnetic resonance imaging (MRI) in participants with active rheumatoid arthritis (RA) (p08136)
NCT01326962	A study of Roactemra/Actemra (tocilizumab) in patients with rheumatoid arthritis who have an inadequate response to DMARDs or anti-TNF
NCT01331837	A study of tocilizumab in comparison to etanercept in participants with rheumatoid arthritis and cardiovascular disease risk factors
NCT01333878	Impact of subcutaneous abatacept in rheumatoid arthritis assessing inhibition of structural damage
NCT01338103	Treatment of pemphigus patients with rituximab 1000mgx2 and assessment of immune status via Cylex
NCT01350804	Efficacy at 24 weeks and safety, tolerability and long term efficacy of secukinumab (ain457) in patients with active rheumatoid arthritis (RA) and an inadequate response to anti-tumor necrosis factor α (Anti-TNFα) agents (CAIN457f2309 and CAIN457f2309e1)
NCT01351480	Benefits of injectable abatacept using magnetic resonance imaging (MRI) in rheumatoid arthritis (RA) patients
NCT01362153	A pharmacokinetic (pk) and pharmacodynamic (pd) study of golimumab in patients with rheumatoid arthritis (RA)
NCT01369017	Effect of interleukin-1 receptor antagonist on inhalation of 20,000 EU clinical CTR reference endotoxin in normal volunteers
NCT01373151	Phase IIB rheumatoid arthritis dose ranging study for BMS-945429 in subjects who are not responding to methotrexate
NCT01374971	Rheumatoid arthritis treatment and biopsy study assessing certolizumab pegol (Cimzia)
NCT01382160	Serum concentration of adalimumab as a predictive factor of clinical outcomes in rheumatoid arthritis (AFORA)
NCT01390441	A study of the pharmacokinetics and safety of mk-8808 (MK-8808-002)
NCT01390545	Velvet, a dose range finding trial of veltuzumab in subjects with moderate to severe rheumatoid arthritis
NCT01394913	Comparison of two etanercept regimens (Reumatocept® versus Enbrel®) for treatment of rheumatoid arthritis
NCT01396317	Study of tocilizumab to treat polymyalgia rheumatica
NCT01399697	A study of Roactemra/Actemra (tocilizumab) in combination with methotrexate versus Roactemra/Actemra monotherapy in patients with rheumatoid arthritis and an inadequate response to methotrexate
NCT01405326	Restore Working Ability in rheumatoid arthritis
NCT01426815	Exploration of TNF-alpha blockade with golimumab in the induction of clinical remission in patients with early peripheral spondyloarthritis (SPA) according to ASAS-criteria

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NCT01439204	Pharmacokinetic study to compare the blood levels of abatacept manufactured at Lonza biologics to the blood levels of abatacept manufactured at the Devens, Massachusetts (MA) facility of Bristol-Myers Squibb
NCT01443364	Open label study to assess the predictability of early response to certolizumab pegol in patients with rheumatoid arthritis
NCT01451203	Efficacy confirmation study of cdp870 in early rheumatoid arthritis
NCT01468077	A study in patients with moderate to severe active rheumatoid arthritis comparing different infusion durations of Roactemra/Actemra (tocilizumab) treatment
NCT01491815	Active conventional therapy compared to three different biologic treatments in early rheumatoid arthritis with subsequent dose reduction
NCT01500278	Study to assess the short- and long-term efficacy of certolizumab pegol plus methotrexate compared to adalimumab plus methotrexate in subjects with moderate to severe rheumatoid arthritis (RA) inadequately responding to methotrexate
NCT01502423	A crossover study of the safety and tolerability of two formulations of adalimumab
NCT01519791	A multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in combination with methotrexate in the treatment of disease modifying antirheumatic drugs (DMARD)-naïve adults with early active rheumatoid arthritis
NCT01521923	A multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in combination with methotrexate in the treatment of disease modifying antirheumatic drugs (DMARD)-naïve adults with early active rheumatoid arthritis
NCT01526057	A pharmacokinetic/pharmacodynamic study comparing pf-05280586 to rituximab in subjects with active rheumatoid arthritis with an inadequate response to TNF inhibitors (reflections b328-01)
NCT01534884	Demonstrate the equivalence of ct-p10 to Mabthera with respect to the pharmacokinetic profile in patients with rheumatoid arthritis
NCT01548768	RHYTHM (formerly Escape II Myocardium)
NCT01557374	Toward the lowest effective dose of abatacept or tocilizumab
NCT01561313	Crossover study of safety and tolerability of two formulations of adalimumab
NCT01566201	Effects of interleukin-1 inhibition on vascular and left ventricular function in rheumatoid arthritis patients with coronary artery disease
NCT01567358	Study of ni-071 in comparison with Remicade in patients with rheumatoid arthritis
NCT01571219	An extension study to demonstrate long-term efficacy and safety of CT-P13 when co-administered with methotrexate in patient with rheumatoid arthritis who were treated with infliximab (Remicade or CT-P13) in study CT-P13 3.1
NCT01578850	Study conducted in subjects with rheumatoid arthritis who have moderate to severe disease activity despite methotrexate therapy with or without other non biologic disease modifying antirheumatic drugs (DMARDs)for at least 12 weeks prior to screening
NCT01587989	A study of Roactemra/Actemra (tocilizumab) with or without methotrexate in patients with mild to moderate rheumatoid arthritis with an inadequate response to methotrexate

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NCT01590966	Scintigraphic detection of the biodistribution of tumor necrosis factor with a radiolabeled anti-TN-Fî± in patients with active rheumatoid arthritis and active axial and peripheral spondyloarthritis
NCT01602302	Ultrasound and withdrawal of biological DMARDs in rheumatoid arthritis
NCT01609205	Doppler evaluation in RA patients after adalimumab
NCT01635686	Comparison the safety and pharmacokinetic characteristics of DWP422 25 mg with those of Enbrel 25MG PFS inj. after subcutaneous injection in healthy male volunteers
NCT01638715	A randomized, multi-center biomarker trial to predict therapeutic responses of patients with rheumatoid arthritis to a specific biologic mode of action
NCT01643928	Rheumatoid arthritis extension trial for subjects who have participated in other PF-05280586 trials (reflections b328-04)
NCT01649804	A long-term safety extension study of WA19926 in participants with rheumatoid arthritis
NCT01657513	TNF-alfa inhibitors and antibody production in patients with psoriasis
NCT01661140	A study of Roactemra/Actemra (tocilizumab) in combination with methotrexate in patients with severe active rheumatoid arthritis, comparing tapering versus maintaining the methotrexate dosage
NCT01664598	An extension study of wa19926 of the long-term safety of Roactemra/Actemra (tocilizumab) in patients with early moderate to severe rheumatoid arthritis
NCT01665430	A long-term extension study to wa19926 of Roactemra/Actemra (tocilizumab) in patients with early, moderate to severe rheumatoid arthritis
NCT01668966	A long term extension study of wa19926 (nct01649804) of tocilizumab (Roactemra/Actemra) in participants with early moderate to severe rheumatoid arthritis
NCT01682512	Efficacy, pharmacokinetics, and safety of bi 695500 in patients with rheumatoid arthritis
NCT01690299	Phase 3b safety and efficacy study of apremilast to treat moderate to severe plaque-plaque psoriasis
NCT01696929	An open-label trial of tocilizumab in schizophrenia
NCT01710358	A study in moderate to severe rheumatoid arthritis
NCT01712178	A study in rheumatoid arthritis (RA) patients to compare two formulations of adalimumab for pharmacokinetic, pharmacodynamic and safety
NCT01715831	A long-term safety extension study of tocilizumab in Brazilian participants with RA having completed the studies ml21530 and ma21488
NCT01715896	A study of mavrilimumab versus anti tumor necrosis factor in subjects with rheumatoid arthritis
NCT01717859	Musculoskeletal ultrasound in predicting early dose titration with tocilizumab
NCT01724268	Corticosteroids and anti TNF in methotrexate inadequate responder rheumatoid arthritis patient
NCT01730456	A long-term extension study of Roactemra/Actemra (tocilizumab) in patients with early moderate to severe rheumatoid arthritis who completed study WA19926

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NCT01734993	A long-term extension study of WA22762 to evaluate safety and efficacy of subcutaneous tocilizumab in participants with moderate to severe rheumatoid arthritis (RA).
NCT01752335	Effect of monoclonal anti-il6 antibody (tocilizumab) on the cardiovascular risk in patients with rheumatoid arthritis
NCT01752855	Study in rheumatoid arthritis for subjects who completed preceding study M13-390 with adalimumab
NCT01758198	Abatacept post-marketing clinical study in Japan
NCT01759030	Study of safety and efficacy of BCD-020 comparing to Mabthera in patients with rheumatoid arthritis
NCT01764997	An evaluation of sarilumab plus methotrexate compared to etanercept plus methotrexate in RA patients not responding to adalimumab plus methotrexate
NCT01765374	Study of sonographic efficacy of rituximab in rheumatoid arthritis
NCT01768572	To evaluate the safety of SAR153191 (REGN88) and tocilizumab added to other RA drugs in patients with RA who are not responding to or intolerant of anti-TNF therapy (SARIL-RA-ASCERTAIN)
NCT01772316	A long-term extension study of wa22763 and na25220 of subcutaneous Roactemra/Actemra (tocilizumab) in patients with moderate to severe rheumatoid arthritis
NCT01782235	Efficacy of tocilizumab in primary Sjögren's syndrome.
NCT01783015	Study of etanercept in subjects with rheumatoid arthritis who have had an inadequate response to adalimumab or infliximab plus methotrexate
NCT01793519	Stopping TNF alpha inhibitors in rheumatoid arthritis
NCT01794117	Anakinra for inflammatory pustular skin diseases
NCT01835613	Evaluation effects of treatment with il-6r inhibitor on clinical response and biomarkers in patients with rheumatoid arthritis (RA) not responding to DMARDs and/or a first biological agent.
NCT01842386	Rituximab for anti-cytokine autoantibody-associated diseases
NCT01844895	Methotrexate-inadequate response autoinjector device sub study
NCT01846975	Introducing a single iv abatacept treatment in RA patients currently receiving weekly sc abatacept to simulate a holiday
NCT01855789	A study of the impact of methotrexate (MTX) discontinuation on the efficacy of subcutaneous tocilizumab with methotrexate in participants with moderate to severe active rheumatoid arthritis
NCT01864265	Prediction of response to certolizumab pegol treatment by functional MRI of the brain
NCT01873443	Long-term efficacy and safety of ct-p10 in patients with RA
NCT01875991	Preference between two autoinjectors in patients with rheumatoid arthritis and plaque psoriasis treated with etanercept
NCT01878318	A study of the effect of Roactemra/Actemra (tocilizumab) in combination with methotrexate on articular damage in the hand in patients with moderate to severe rheumatoid arthritis who have an inadequate response to non-biological DMARDs

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NCT01890473	Study to characterize the pharmacokinetics of a single dose of sc abatacept 125 mg using the bd autoinjector or the prefilled syringe
NCT01893996	Study of adalimumab to lower cardiovascular risk in RA patients with well controlled joint disease
NCT01895309	A study comparing sb4 to Enbrelâ® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
NCT01901185	Study to evaluate the ability of subjects with rheumatoid arthritis or psoriatic arthritis to effectively use a reusable autoinjector to self-inject etanercept
NCT01927263	A phase 3 study of ni-071 in patients with rheumatoid arthritis
NCT01927757	Evaluating etanercept use in patients with moderate to severe rheumatoid arthritis who have lost response to adalimumab
NCT01936181	A study comparing SB2 to Remicade® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
NCT01941095	A study of subcutaneously administered Roactemra/Actemra (tocilizumab) in patients with rheumatoid arthritis
NCT01941940	A study to evaluate efficacy of tocilizumab administered as monotherapy or in combination with methotrexate and/or other disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) participants
NCT01951170	An open-label study of Roactemra/Actemra (tocilizumab) in patients with moderate to severe active rheumatoid arthritis
NCT01954979	A phase i study of abatacept in the treatment of patients with steroid refractory chronic graft versus host disease (CGVHD)
NCT01962974	A golimumab phase 3b, multicenter, assessment of intravenous efficacy in rheumatoid arthritis subjects who have diminished disease control despite treatment with infliximab (Remicadeâ®)
NCT01969409	Autoantibody reduction therapy in patients with idiopathic pulmonary fibrosis
NCT01970475	Efficacy and safety study of ABP 501 compared to adalimumab in subjects with moderate to severe rheumatoid arthritis
NCT01987479	The safety and efficacy of Roactemra/Actemra alone or in combination with non-biologic antirheumatics in rheumatoid arthritis patients.
NCT01999868	Efficacy of ustekinumab followed by abatacept for the treatment of psoriasis vulgaris
NCT02001987	A study of Roactemra/Actemra (tocilizumab) in tocilizumab-naive patients with rheumatoid arthritis with inadequate response to non-biologic disease-modifying antirheumatic drugs (DMARDs) or biologic therapy
NCT02010216	A study of Roactemra/Actemra (tocilizumab) in adult patients with rheumatoid arthritis (SVOBODA Programme)
NCT02018042	An open-label single-arm clinical trial to evaluate the efficacy of abatacept in moderate to severe patch type alopecia areata
NCT02019472	A study comparing sirukumab (CNTO 136) monotherapy with adalimumab (Humira®) monotherapy in the treatment of active rheumatoid arthritis

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NCT02019602	A multicener, postmarketing study evaluating the transfer of Cimzia from the mother to the infant via the placenta
NCT02027298	Abatacept for patients with inflammatory arthritis associated with Sjögren's syndrome: an open-label phase II study
NCT02035800	Bone resorption, osteoclastogenesis and adalimumab
NCT02053727	Abatacept vs placebo in RA patients with hepatitis B on entecavir background
NCT02056184	Targeted ultrasound in rheumatoid arthritis
NCT02067910	Efficacy and safety of abatacept in patients with primary Sjögren's syndrome
NCT02079532	A study of Mabthera (rituximab) in patients with rheumatoid arthritis who have had an inadequate response to a single anti-TNF inhibitor
NCT02090101	Study evaluating the influence of lv5fu2 bevacizumab plus anakinra association on metastatic colorectal cancer
NCT02092467	Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis
NCT02092961	Randomised double-blind, placebo-controlled, parallel group study in patients with active rheumatoid arthritis: magnetic resonance imaging sub-study
NCT02097264	A trial investigating the mechanism of action of NNC0109-0012 (anti-IL-20 MAB) through synovial biopsies in subjects with rheumatoid arthritis and an inadequate response to methotrexate
NCT02097524	Single-dose study to describe the pharmacodynamics (pd) and safety of sarilumab (regn88/ sar153191) and tocilizumab in adults with rheumatoid arthritis (RA)
NCT02097745	A study of the efficacy and safety of re-treatments with rituximab in patients with active rheumatoid arthritis who have had an inadequate response to anti-TNFa therapies
NCT02109289	Etanercept in rheumatoid arthritis and vascular inflammation
NCT02114931	Long-term safety and efficacy of ABP 501 in subjects with moderate to severe rheumatoid arthritis
NCT02115750	Comparison of CHS-0214 to Enbrel (etanercept) in patients with rheumatoid arthritis (RA)
NCT02116504	Anti-biopharmaceutical immunization: prediction and analysis of clinical relevance to minimize the risk of immunization in rheumatoid arthritis patients or juvenile idiopathic arthritis patients
NCT02132234	Effects of biological treatment on blood pressure and endothelial function in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
NCT02137226	BI 695501 compared to adalimumab in patients with active rheumatoid arthritis
NCT02141997	A study to investigate the safety and efficacy of ABT-122 given with methotrexate in subjects with active rheumatoid arthritis who have an inadequate response to methotrexate
NCT02148640	The NOR-SWITCH study
NCT02148718	Rapidity of response to adalimumab treatment in patients with Crohn's disease
NCT02149121	Pk similarity prospective phase 3 study in patients with rheumatoid arthritis

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NCT02150473	The effect of adalimumab plus methotrexate (MTX) versus placebo plus MTX on cartilage in (RA) patients
NCT02151851	A study of certolizumab pegol as additional therapy in Chinese patients with active rheumatoid arthritis
NCT02154425	A multicenter, postmarketing study evaluating the concentration of Cimzia® in mature breast milk of lactating mothers
NCT02167139	A study comparing SB5 to Humira® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
NCT02175056	A dose-block randomized, placebo controlled (double-blind), active controlled(open-label), dose-escalation study
NCT02187055	An efficacy and safety study evaluating tofacitinib with and without methotrexate compared to adalimumab with methotrexate
NCT02198651	A phase 4 trial assessing the impact of Residual Inflammation Detected Via Imaging techniques, Drug Levels and Patient Characteristics on the Outcome of Dose tapering of Adalimumab in Clinical Remission Rheumatoid arthritis (RA) subjects (PREDICTRA)
NCT02222493	A study of pf-06438179 (infliximab-Pfizer) and infliximab in combination with methotrexate in subjects with active rheumatoid arthritis (reflections B537-02).
NCT02232880	Treatment of resistant hypertension by prevention of t-cell co-stimulation
NCT02236481	Clinical study to evaluate the efficacy of anakinra in patients with rheumatoid arthritis and diabetes
NCT02242474	Anti-TNF use during elective foot and ankle surgery in patients with rheumatoid arthritis
NCT02260791	A study to compare FKB327 efficacy and safety with Humira® in rheumatoid arthritis patients
NCT02287922	A phase IIb study for alx-0061 monotherapy in subjects with rheumatoid arthritis
NCT02293590	Rice: remission by intra-articular injection plus certolizumab
NCT02296775	Comparative pharmacokinetic, pharmacodynamic, safety and efficacy study of three anti-cd20 monoclonal antibodies in patients with moderate to severe rheumatoid arthritis
NCT02304354	Relationship between t lymphocytes depletion and clinical response to rituximab in rheumatoid arthritis (Lyritux)
NCT02308163	A study to evaluate safety and efficacy of asp015k in patients with rheumatoid arthritis (RA) who had an inadequate response to DMARDs
NCT02319642	An open-label extension study of certolizumab pegol in Chinese patients with rheumatoid arthritis who enrolled in RA0044
NCT02332590	Efficacy and safety of sarilumab and adalimumab monotherapy in patients with rheumatoid arthritis (SARIL-RA-MONARCH)
NCT02353780	Mechanistic studies of b- and t-cell function in RA patients treated with TNF antagonists, tocilizumab, or abatacept

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NCT02357069	A study comparing lbec0101 to Enbrelâ® in subjects with active rheumatoid arthritis despite methotrexate therapy
NCT02371096	Comparative pharmacokinetic trial of rgb-03 and Mabthera
NCT02373813	Study of etanercept monotherapy vs methotrexate monotherapy for maintenance of rheumatoid arthritis remission
NCT02374021	Treatments against RA and effect on FDG-PET/CT
NCT02376335	B-cell depleting therapy (rituximab) as a treatment for fatigue in primary biliary cirrhosis
NCT02378506	Study to assess the immunogenicity, safety, and efficacy of high capacity process etanercept in rheumatoid arthritis subjects
NCT02393378	Namilumab vs adalimumab in participants with moderate to severe early rheumatoid arthritis inadequately responding to methotrexate
NCT02404558	Single-dose study to describe the safety of sarilumab and tocilizumab in patients with rheumatoid arthritis
NCT02405780	A study to compare FKB327 long-term safety, efficacy and immunogenicity with Humira® in rheumatoid arthritis patients
NCT02429934	Abatacept for SLE arthritis (im101-330)
NCT02430909	Multiple dose study of ucb4940 as add-on to certolizumab pegol in subjects with rheumatoid arthritis
NCT02433184	Very early versus delayed etanercept in patients with RA
NCT02451839	An observational study of the effectiveness of adalimumab on health and disability outcomes in New Zealand patients with immune-mediated inflammatory diseases (VITALITY)
NCT02466581	Dose reduction for early rheumatoid arthritis patients with low disease activity
NCT02468791	MabionCD20® compared to Mabthera® in patients with rheumatoid arthritis
NCT02480153	A study of PF-06410293 (adalimumab-Pfizer) and adalimumab (Humira) In combination with methotrexate in subjects with active rheumatoid arthritis (REFLECTIONS B538-02)
NCT02481180	Tolerance, pharmacokinetics and preliminary efficacy of t0001 in RA (rheumatoid arthritis)
NCT02495129	Study of pharmacodynamic effects of vay736 in patients with primary Sjögren's syndrome
NCT02504268	Effects of abatacept in patients with early rheumatoid arthritis
NCT02514772	Gp2013 treatment in patients with active rheumatoid arthritis, previously treated with Rituxan® or Mabthera®
NCT02526992	Evaluation by HR-pqct of bone microarchitecture changes in patients with rheumatoid arthritis under anti-TNF therapy
NCT02547493	Vaccination against pneumococcal in naïve abatacept rheumatoid arthritis patients
NCT02557100	Study to assess changes in the immune profile in adults with early rheumatoid arthritis

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NCT02565810	An multicentre clinical study to evaluate the usability and safety of the pre-filled pen and pre-filled syringe of SB5 in subjects with rheumatoid arthritis
NCT02573012	Study to compare the efficacy of tocilizumab with or without glucocorticoid discontinuation in rheumatoid arthritis participants
NCT02616380	Real-world outcome of adalimumab on rheumatoid arthritis patients in Taiwan
NCT02629159	A study comparing ABT-494 to placebo and to adalimumab in subjects with rheumatoid arthritis who are on a stable dose of methotrexate and who have an inadequate response to methotrexate
NCT02631538	Safety and efficacy study of subcutaneous belimumab and intravenous rituximab co-administration in subjects with primary Sjögren's syndrome
NCT02638259	Comparative efficacy and safety study of gp2015 and Enbrel® in patients with rheumatoid arthritis
NCT02640612	Long-term assessment of safety and efficacy of BI 695501 in patients with rheumatoid arthritis
NCT02652273	Inhibition of co-stimulation in rheumatoid arthritis
NCT02659150	Effect of subcutaneous Actemra on inflamed atherosclerotic plaques in patients with rheumatoid arthritis
NCT02682823	Tocilizumab real-life human factors (RLHFS) validation study
NCT02683564	Bow015 (infliximab-epirus) and infliximab in patients with active rheumatoid arthritis: the uniform study
NCT02693210	A study to evaluate the efficacy and safety of Mabthera alone and in combination with either cyclophosphamide or methotrexate in patients with rheumatoid arthritis
NCT02714634	Clinical trial evaluating methotrexate + biologic versus methotrexate, salazopyrine and hydroxychloroquine in patients with rheumatoid arthritis and insufficient response to methotrexate
NCT02714881	Lipids, inflammation, and CV risk in RA
NCT02715908	A study to evaluate the long-term safety and efficacy of lbec0101 in subjects with active rheumatoid arthritis despite methotrexate (MTX)
NCT02722044	Usability of an AI for M923 in subjects with moderate to severe RA
NCT02722694	A phase 3 study of abatacept in chinese patients with active rheumatoid arthritis and inadequate response to methotrexate
NCT02731560	Rituximab (rtx) for disease modifying anti rheumatic drug (DMARD) non-responders in Pakistan: the Pakistan rituximab study (PaRiS)
NCT02743390	Effects of the TNF-alpha inhibitIon on hemodynamic parameters in resistant hypertension
NCT02744196	Clinical trial to evaluate efficacy and safety of Acellbia® (JSC "Biocad") with methotrexate in first line biological therapy of patients with active rheumatoid arthritis
NCT02744755	Clinical trial to compare treatment with GP2017 and Humira® in patients with rheumatoid arthritis
NCT02746380	A study comparing LBAL to Humira® in subjects with active rheumatoid arthritis despite methotrexate therapy

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NCT02760407	Evaluation of the effectiveness and safety of two dosing regimens of Olokizumab (OKZ), compared to placebo and adalimumab, in subjects with rheumatoid arthritis (RA) who are taking methotrexate but have active disease
NCT02762838	Comparative clinical trial of efficacy and safety of BCD-055 and Remicade® in combination with methotrexate in patients with active rheumatoid arthritis
NCT02765074	Filling bone erosions: a longitudinal multicentric HR-PQCT study of subcutaneous tocilizumab in rheumatoid arthritis
NCT02770794	Optimization of infliximab withdrawal strategy for rheumatoid arthritis
NCT02778906	Abatacept reversing subclinical inflammation as measured by MRI in ACPA positive arthralgia
NCT02779114	Retro (reduction of therapy in RA patients in ongoing remission)
NCT02780583	Treatment of macrophage activation syndrome (mas) with anakinra
NCT02792699	Study to assess if ABP798 is safe & effective in treating moderate to severe rheumatoid arthritis compared to rituximab
NCT02805010	Pharmacokinetics, safety and tolerability study of single dose of abatacept 125mg administered subcutaneously
NCT02819726	A study to compare the pharmacokinetics, pharmacodynamics, safety, and efficacy of sait101 versus Mabthera® versus Rituxan® in patients with rheumatoid arthritis (RA)
NCT02833350	Safety and efficacy study of GDC-0853 compared with placebo and adalimumab in participants with rheumatoid arthritis (RA)
NCT02837146	Ultrasound as imaging biomarker of early response to tocilizumab and methotrexate in very early rheumatoid arthritis
NCT02840175	Treatment tapering in JIA with inactive disease
NCT02843789	Evolution of adipokines and body composition in rheumatoid arthritis patients receiving tocilizumab therapy
NCT02862574	GS-5745 as add-on therapy to a tumor necrosis factor inhibitor and methotrexate regimen in adults with moderately to severely active rheumatoid arthritis
NCT02889796	Filgotinib in combination with methotrexate in adults with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate
NCT02908217	Safety and efficacy of tocilizumab versus placebo in polymyalgia rheumatica with glucocorticoid dependence semaphore
NCT02915159	A study to assess the efficacy and safety of abatacept in adults with active primary Sjögren's syndrome
NCT02935387	Remission induction in very early rheumatoid arthritis
NCT02937701	Study to assess if abp710 is safe & effective in treating moderate to severe rheumatoid arthritis compared to infliximab
NCT02986139	Assess the injection site pain associated with a new etanercept formulation in adult subjects with RA or PSA

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NCT02990806	A phase 3 study of ni-071 in patients with rheumatoid arthritis (RADIANCE)
NTR1011	Hypothesis generating study to identify the changes in synovial tissue early after initiation of infliximab therapy
NTR1088	Sevra-trial safety and efficacy of vaccination with t cell-dependent and t cell-independent primary and recall antigens in patients with rheumatoid arthritis treated with anti TNF-á antibodies (adalimumab) and anti B cell therapy (rituximab).
NTR1137	An open-label pilot study on the effects of trivalent inactivated influenza vaccination (Influvac®) in rheumatoid arthritis patients treated with rituximab.
NTR1210	Exploratory trial on intra-articular etanercept treatment in inflammatory arthritis
NTR144	Strategies in early arthritis management.
NTR1605	(English) Cost-effectiveness of new medicines (Mabthera and Orencia) compared to a second TNF blocking medicine, for patients with inadequate effect of a first TNF blocking medicine. (Dutch) Onderzoek naar de kosteneffectiviteit van nieuwe medicijnen (Mabthera en Orencia) vergeleken met een tweede TNF blokerend middel, voor patienten met onvoldoende effect van een eerste behandeling met TNF blokkerende middelen.
NTR2911	Tocilizumab met biopten cohort. Tocilizumab with biopsy cohort.
NTR3216	Onderzoek naar non inferioriteit van afbouw en stop behandelstrategieën van adalimumab of etanercept bij patiënten met reumatoïde artritis: kosten besparen tegen welke prijs?
NTR3327	Influence of rituximab on endothelial dysfunction in RA.
NTR3509	Therapeutic drug monitoring: toward tailored dosing of adalimumab in rheumatoid arthritis
NTR383	The efficacy and safety of intra-articular injections with the TNF-a antagonist infliximab in patients with chronic or recurrent arthritis of the knee.
NTR3903	Dose-to-target of etanercept treatment in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.
NTR5279	The effect of switching treatment from innovator infliximab to infliximab biosimilar on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, spondyloarthritis or psoriatic arthritis in daily clinical care
NTR801	IMPROVED: Induction therapy with methotrexate and prednisone in rheumatoid or very early arthritic disease
NTR851	Prospective study on the effects of rituximab on synovial tissue of patients with rheumatoid arthritis.
NTR859	Identification of predictive factors in synovial samples for the clinical response to TNF-alpha blockade in rheumatoid arthritis.
SLCTR/2008/008	Efficacy of low dose rituximab with methotrexate compared to leflunomide with methotrexate in patients with refractory rheumatoid arthritis: a randomized double blind controlled clinical trial

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Appendix 3. Summary of safety warnings from regulatory agencies

Abatacept

No recent warnings have been issued with regard to abatacept. On the product label of abatacept, the FDA warns against known safety implications reporting, "In controlled clinical trials, patients receiving concomitant abatacept and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively). Concurrent administration of a TNF antagonist with abatacept has been associated with an increased risk of serious infections and no statistically significant additional benefit over use of the TNF antagonists alone" (FDA 2007). Furthermore, the FDA reports that, "rare occurrences of anaphylaxis or anaphylactoid reactions have been observed in two of 2,688 patients treated with abatacept in clinical trials" (FDA 2007). Trials have also shown that, "COPD patients treated with abatacept developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea" (FDA 2007).

The effects of abatacept on pregnant women, pediatric patients, and the development of malignancies is "not yet fully understood" (FDA 2007). The European Medicines Agency (EMA) reports the adverse reactions in patients treated with abatacept, ranking the occurrences of such reactions as very common (≤ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000). EMA 2009a reports increase in blood pressure, abnormal liver function test (transaminases increased) and headaches are very common adverse reactions. Dizziness, cough, rash including dermatitis, diarrhea, nausea, dyspepsia, abdominal pain, lower respiratory tract infection (including bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection, hypertension, flushing, fatigue and asthenia are common (EMA 2009a). Overall, "the most commonly reported adverse events (occurring in 10% or more of patients) were headaches, upper respiratory tract infection, nasopharyngitis, and nausea. The adverse events most commonly resulting in clinical intervention were due to infection" (FDA 2007).

Adalimumab

The updated 2008 FDA label for adalimumab reports "Serious infections, sepsis, tuberculosis and cases of opportunistic infections, including fatalities, have been reported with the use of TNF blocking agents including Humira® [adalimumab]" (FDA 2008b). "Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalization or fatal outcomes associated with infections have been reported" (EMA 2009b). Furthermore, hepatitis B reactivation has been shown to be associated with adalimumab treatment (Health Canada 2006a). The FDA reports, "As observed with other TNF blocking agents, tuberculosis associated with the administration of Humira® in clinical trials has been reported" (FDA 2008b).

In rare instances, adalimumab has been associated with, "new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease including multiple sclerosis" (EMA 2009b). Furthermore, "In the controlled portions of clinical trials of some TNF-blocking agents, including Humira, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients" (FDA 2008b).

"Some of these hepatosplenic T-cell lymphomas have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for Crohn's disease". Thus, the risk of the development of hepatosplenic T-cell lymphoma cannot be excluded for patients treated with adalimumab (EMA 2009b). Though the causal relationship of hematological reactions and the use of adalimumab remain unclear as of 2008, the FDA label states, "Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents". Furthermore, the FDA reports "Treatment with Humira® [adalimumab] may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome" (FDA 2008b).

Anakinra

Anakinra leads to an increased rate of infections (2%) versus placebo (less than 1%). Following the EMEA standard of classification of frequency of the occurrence of "undesirable effects" mentioned above, neutropenia and serious infection requiring hospitalization were common (between 1/10 and 1/100) and headaches and injection site reactions were very common occurring in 1/10 or more patients treated with anakinra (EMA 2004). "A… clinical trial sponsored by Amgen Inc. showed a higher incidence of serious infection and of neutropenia in anakinra and etanercept combination group than patients receiving Enbrel [etanercept] alone and higher than observed in previous trials where Kineret [anakinra] was used alone (EMA 2003), therefore, the use of etanercept and anakinra is not recommended as it leads to safety complications)". Furthermore, the FDA reports in its most recent report on anakinra that "Hypersensitivity reactions associated with Kineret [anakinra] administration are rare" (FDA 2001). Moreover, the FDA reports the effects of anakinra on the hematologic conditions of patients stating that, "In placebo-controlled studies with Kineret® [anakinra], treatment was associated with small reductions in the mean values for total white blood count, platelets, and absolute neutrophil count (ANC), and a small increase in the mean eosinophil differential percentage" (FDA 2001). With regard to the development of malignancies for patients treated with anakinra, trials show that, "among 5300 RA patients treated with Kineret [anakinra] clinical trials for a mean of 15 months (approximately 6400 patient years of treatment), lymphomas were observed for a rate of 0.12 cases per 100 patient years. This is 3.6 fold higher than the rate of lymphomas expected in the general population, based on the National Cancer Institutes Surveillance Epidemiology and End Results (SEER) database" (FDA 2001).

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Etanercept

In the post-marketing reports of etanercept, "Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with Enbrel® [etanercept]" (FDA 2008d). Furthermore, "Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with Enbrel® than with TNF-blocking monoclonal antibodies. Nonetheless, post-marketing cases of tuberculosis reactivation have been reported for TNF blockers, including Enbrel® [etanercept]. Patients receiving Enbrel® should be monitored closely for signs and symptoms of active tuberculosis. The possibility of tuberculosis should be considered, especially in patients who have travelled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with Enbrel® should have a thorough history taken prior to initiating therapy" (FDA 2008d). This finding is also stated in an important health warning issued by Health Canada in 2006 (Health Canada 2006a).

Furthemore, etanercept has been associated with the risk of histoplasmosis and other invasive fungal infections. Health Canada 2009 states, "...although no histoplasmosis infections were reported among 17,696 patients from the United States and Canada who were treated with Enbrel®, in 38 clinical trials and four cohort studies involving all authorized indications, post marketing cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including Enbrel®." The FDA also outlines the risk of nervous system complications stating, "nervous system complications such as multiple sclerosis, seizures, or inflammation of the nerves of the eyes have occurred in rare cases" (FDA 2008d).

Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with Enbrel® [etanercept] (FDA 2008d). The FDA reports on the risk of malignancies for patients on etanercept treatment, stating "Patients have been observed in clinical trials with Enbrel® for over five years. Among 4462 rheumatoid arthritis patients treated with Enbrel® in clinical trials for a mean of 27 months (approximately 10000 patient-years of therapy), lymphomas were observed for a rate of 0.09 cases per 100 patient-years. This is 3-fold higher than the rate of lymphomas expected in the general population based on the Surveillance, Epidemiology, and End Results Database. Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with Enbrel®" (FDA 2008d). The FDA also reports, "Treatment with Enbrel® may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome or autoimmune hepatitis which may resolve following withdrawal of Enbrel®" (FDA 2008d).

The use of etanercept has also been associated with the relapse of hepatitis B (Health Canada 2006a).

Infliximab

In its recent revised report on infliximab, the EMEA reports on the risk of infusion reactions and hypersensitivity, stating, "An infusion-related reaction was defined in clinical studies as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. In clinical studies, approximately 20% of infliximab-treated patients compared with approximately 10% of placebo-treated patients experienced an infusion-related effect. Approximately 3% of patients discontinued treatment due to infusions reactions" (EMA 2009a). Infliximab is also associated with the relapse of hepatitis B as reported by Health Canada in 2006 (Health Canada 2006a). "Opportunistic infections have been reported in patients treated with infliximab, suggesting that host defence against infection is compromised. It should be noted that suppression of TNF-alpha may also mask symptoms of infection such as fever." There is also a possible association between infliximab and heptosplenix T-Cell lymphoma in pediatric and young adult patients with Crohn's disease (Health Canada 2006b).

"In a study designed to evaluate Remicade® [infliximab] in congestive heart failure (CHF), 150 patients with moderate to severe (NYHA class II-IV) CHF were treated with three infusions of Remicade 5mg/ kg, or placebo over six weeks. Higher incidences of mortality and hospitalization for worsening heart failure were seen in those patients treated with Remicade®, especially have treated with the higher dose of 10mg/kg. At present 7 out of 101 patients treated with Remicade® have died compared to no deaths among 49 patients on placebo" (EMA 2001). In a May 2009 revision of the Remicade label, the FDA warns, "Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving TNF- blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported. Patients have frequently presented with disseminated rather than localized disease, and are often taking concomitant immunosuppressants such as methotrexate or corticosteroids with Remicade®" (FDA 2009a). In an investigation of neurological events, EMEA reports "Infliximab and other agents that inhibit TNF-alpha have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome" (EMA 2009a).

The increased risk of developing lymphoma is also reported. FDA archived report from October 2004 on infliximab safety alerts notifies that

"During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis and Crohn's disease, 1 patient developed lymphoma among 1389 REMICADE-treated patients versus 0 among 483 control patients (median duration of follow-up 1.1 years)." " In the controlled and open-label portions of these clinical trials of REMICADE, 3 patients developed lymphomas (1 patient with rheumatoid arthritis and 2 patients with Crohn's disease) among 2410 patients (median duration of follow-up 1.1 years)." "As a result of this evaluation, a warning concerning malignancy has been added to the labelling for all therapeutic agents that block TNF."(FDA 2004).

Another evidence of infliximab associated with lymphoma states that "In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients... In the

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combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately 4-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies**,** may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy" (EMA 2009a).

TNF-blockers as a group

In 2008, the FDA issued a safety alert regarding anti-TNF biologics, which stated that the risk of pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis and other opportunistic infections were not consistently recognized in patients taking tumor necrosis factor-alpha blockers (TNF blockers including etanercept, adalimumab, infliximab or certolizumab), which resulted in the delay of proper antifungal treatment and at times led to death (FDA 2008c). The FDA reviewed 240 reports of histoplasmosis, an infection caused by the fungus Histoplasma capsulatum, in patients being treated with Enbrel, Humira, or Remicade. The majority of the reports involved people in the Ohio River and Mississippi River valleys (the fungus is commonly found in those areas). In at least 21 of the reports, histoplasmosis was initially not recognized by healthcare professionals, and antifungal treatment was delayed. Twelve of those patients died. The FDA recommended that for patients at risk of histoplasmosis and other invasive fungal infections, clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. In 2004, the FDA issues a safety alert regarding risk of cancer with anti-TNF biologics (FDA 2004). According to the FDA "In the controlled portions of clinical trials of all the TNFα-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis and Crohn's disease, 1 patient developed lymphoma among 1389 REMICADE-treated patients versus 0 among 483 control patients (median duration of follow-up 1.1 years). In the controlled and open-label portions of these clinical trials of REMICADE, 3 patients developed lymphomas (1 patient with rheumatoid arthritis and 2 patients with Crohn's disease) among 2410 patients (median duration of follow-up 1.1 years). In rheumatoid arthritis patients, this is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis and Crohn's disease, this is approximately 6-fold higher than expected in the general population."

Rituximab

While no reviews exist for rituximab in the EMEA web site and Health Canada's reviews are outdated, the FDA provides its most recent safety information for Rituxan® [rituximab] from 2009. Rituxan was found to be associated with progressive multifocal leukoencephalopathy. FDA and Genetech notified: "A third case of progressive multifocal leukoencephalopathy (PML) has been reported in a patient with rheumatoid arthritis treated with Rituxan." In view of this event, Genetech has advised physicians to have high index of suspicion for PML stated as "Physicians should consider PML in any patient being treated with Rituxan who presents with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, Rituxan should be discontinued." (FDA 2009b). Another event associated with Rituxan was notified in a FDA label from 2008. In this label, the possible safety complications of Rituxan® use included "tumor lysis syndrome which necessitates clinicians to administer prophylaxis and monitor patients renal function, hepatitis B reactivation with fulminant hepatitis, which can sometimes [be] fatal and the risk of progressive multifocal leukoencephalopathy" (Drugs 2006).

FDA and Genentech informed healthcare professionals of important emerging safety information about Rituxan®. "Two patients died after being treated with Rituxan® for systemic lupus erythematosus (SLE). Rituxan® is approved for the above indication and is prescribed off-label for other serious diseases and conditions such as SLE. The cause of death was progressive multifocal leukoencephalopathy, a viral infection of the brain (that is caused by reactivated JC virus which is present in about 80% of adults" (FDA 2006). Further risks include "cardiac arrhythmias and angina" which can be life threatening, and "bowel obstruction and perforation" (FDA 2008d). Health Canada 2006a also provided warnings of bowel obstruction and perforation, "Reports of abdominal pain, bowel obstruction, and perforation, in some cases leading to death, have been observed in patients receiving Rituxan®. The majority of reports, including all deaths, have occurred in patients receiving Rituxan in combination with chemotherapy for NHL [(non-Hodgkin's Lymphoma)] indication. A causal relationship has not been established".

Tofacitinib

The FDA issued a Risk Evaluation and Mitigation Strategy (REMS) document, a modification in February 2015 to the original 11/2012 document, highlighting the known concerns with tofacitinib, instructing the pharmaceutical company to send information to physicians and pharmacists regarding the risk of serious infections, malignancies, decreases in peripheral lymphocyte counts, neutrophil counts, hemoglobin, and increases in lipid parameters in peripheral blood with XELJANZ (tofacitinib) (FDA 2015).

WHAT'S NEW

Date	Event	Description
22 June 2015	New search has been performed	New citation: conclusions changed, description: Original review of biologics in RA split into four by the patient populations

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Date	Event	Description
		1. MTX-naive; 2. biologic + MTX/other DMARDs in MTX/other DMARD failure; 3. biologic monotherapy in MTX/other DMARD failure; and 4. biologic-experienced. This review presents comparisons of comparisons of biologic (with or without concurrent methotrexate) versus a) placebo and b) head-to-head studies against other traditional DMARDs in a RA patient population who have previously experienced and been unsuccessfully treated with biologics.
22 June 2015	New citation required and conclusions have changed	New search with 9 new studies included

H I S T O R Y

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Date	Event	Description
15 January 2013	Amended	Minor edits
25 February 2010	Amended	CMSG ID: C187-R

C O N T R I B U T I O N S   O F   A U T H O R S

JS - study concept

JS, GW - protocol development

JS, PT, GW, EG - protocol editing

JS, EG, AM - data extraction

AH, GW, JS, AM - data analysis

JS - First draft of the review and NMA

All authors - Revision of the manuscript, and approval of the final version

D E C L A R A T I O N S   O F   I N T E R E S T

JS - JS has received research grants from Takeda and Savient and consultant fees from Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology. JS serves as the principal investigator for an investigator-initiated study funded by Horizon pharmaceuticals through a grant to DINORA, Inc., a 501 (c)(3) entity. JS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies; a member of the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC); Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee; and a member of the Veterans Affairs Rheumatology Field Advisory Committee.

AH - none

AM - none

EG - none

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NOTES

None

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